ClinicalEvidence

Panic disorder

Search date June 2007

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ABSTRACT

INTRODUCTION: Panic disorder occurs in up to 3% of the adult population at some time, and is associated with other psychiatric and personality disorders, and with drug and alcohol abuse. The risk of suicide and attempted suicide has been found to be higher in people with panic disorder than in people with other psychiatric illness, including depression. METHODS AND OUTCOMES: We conducted a systematic review and aimed to answer the following clinical questions: What are the effects of non-drug treatments for panic disorder? What are the effects of drug treatments for panic disorder? What are the effects of combined drug and psychological treatments for panic disorder? We searched: Medline, Embase, The Cochrane Library, and other important databases up to June 2007 (Clinical Evidence reviews are updated periodically; please check our website for the most up-to-date version of this review). We included harms alerts from relevant organisations such as the US Food and Drug Administration (FDA) and the UK Medicines and Healthcare products Regulatory Agency (MHRA). RESULTS: We found 36 systematic reviews, RCTs, or observational studies that met our inclusion criteria. We performed a GRADE evaluation of the quality of evidence for interventions. CONCLUSIONS: In this systematic review, we present information relating to the effectiveness and safety of the following interventions: applied relaxation; benzodiazepines; breathing retraining; brief dynamic psychotherapy; buspirone; client-centred therapy; cognitive behavioural therapy (CBT) (alone or plus drug treatments); cognitive restructuring; couple therapy; exposure (external or interoceptive); insight-orientated therapy; monoamine oxidase inhibitors (MAOIs); psychoeducation; selective serotonin reuptake inhibitors (SSRIs); self-help; and tricyclic antidepressants (imipramine).

QUESTIONS

INTERVENTIONS

NON-DRUG TREATMENTS FOR PANIC DISORDER

DRUG TREATMENTS FOR PANIC DISORDER

COMBINED TREATMENTS FOR PANIC DISORDER

To be covered in future updates

Clonidine

Key points

- Panic disorder is characterised by recurrent, unpredictable panic attacks, making people worry about or change their behaviour to avert subsequent panic attacks or their consequences.

  Panic disorder occurs in up to 3% of the adult population at some time, and is associated with other psychiatric and personality disorders, and with drug and alcohol abuse.

The risk of suicide and attempted suicide has been found to be higher in people with panic disorder than in people with other psychiatric illness, including depression.

- CBT is effective in reducing symptoms of panic disorder over 6 months or longer, but we don't know whether it is more effective than other psychological treatments.

  CBT is more effective than waiting list and other controls in reducing symptoms in panic disorder with or without mild to moderate agoraphobia.

  We don't know whether CBT alone is more effective than antidepressants alone, but weak evidence suggests that the effects of CBT may last longer. Combined treatment with CBT plus antidepressants has shown to be more effective than CBT alone or antidepressants alone in reducing symptoms in the short term.

- Other forms of psychotherapy can also be beneficial in reducing symptoms associated with panic disorder, with or without drug treatments.

  Applied relaxation, client-centred therapy, cognitive restructuring, and exposure to the panic-inducing stimulus are all likely to be effective in reducing symptoms.

  Self-help using CBT techniques may be as effective as therapist-based CBT.

  Breathing retraining, couple therapy, insight-orientated therapy, psychoeducation, and brief dynamic psychotherapy may be beneficial, but we found insufficient evidence to be sure.

- SSRIs and tricyclic antidepressants are also effective at reducing the symptoms of panic disorder.

  Benzodiazepines can be effective in reducing symptoms in panic disorder, but their adverse-effect profile makes them unsuitable for long-term treatment.

  We don't know whether buspirone or MAOIs are effective.

DEFINITION

A panic attack is a period in which there is sudden onset of intense apprehension, fear, or terror, often associated with feelings of impending doom. Panic disorder is classified by the DSM-IV as recurrent, unpredictable panic attacks followed by at least 1 month of persistent concern about having another panic attack, worry about the possible implications or consequences of the panic attacks, or a significant behavioural change related to the attacks. The term "panic disorder" excludes panic attacks attributable to the direct physiological effects of a general medical condition, a substance, or another mental disorder. [1] The ICD-10 classifies panic disorder as recurrent, unpredictable panic attacks, with sudden onset of palpitations, chest pain, choking sensations, dizziness, and feelings of unreality, often with associated fear of dying, losing control, or going mad, but without the requirement for the symptoms to have persisted for 1 month or longer. The DSM-IV classifies these conditions as primarily panic disorder with or without agoraphobia, [1] whereas the ICD-10 classifies them as primarily agoraphobia with or without panic disorder. [2] The diagnosis should not be made in people with co-morbid depression, when the panic is considered to be secondary to depression. [2] **Diagnosis:** Although panic attacks are a necessary feature of panic disorder, panic attacks on their own are not enough to make the diagnosis. Panic attacks may happen in the context of specific situations such as social or specific phobia which are different from panic disorder. [1] A diagnosis of panic disorder is made in the presence of recurrent unexpected panic attacks followed by at least 1 month of persistent concern about having another panic attack. [1]

INCIDENCE/ PREVALENCE

Panic disorder often starts at about 20 years of age (between late adolescence and the mid-30s). [3] Lifetime prevalence is 1% to 3%, and panic disorder is more common in women than in men. [4] An Australian community study found 1-month prevalence rates for panic disorder (with or without agoraphobia) of 0.4% using ICD-10 diagnostic criteria, and of 0.5% using DSM-IV diagnostic criteria. [5] One systematic review of observational data estimated the prevalence rate of panic disorder during the perinatal period at between 1.3% to 2.0%, and that, although the symptoms of panic during pregnancy may be identical to at other periods, they are often interpreted in the context of the perinatal state (e.g., a woman may interpret panic attacks during pregnancy as an indication that something is wrong with the pregnancy). [6]

AETIOLOGY/ RISK FACTORS

The onset of panic disorder tends to be preceded by stressful life events, [7] [8] although a negative interpretation of these events, in addition to their occurrence, has been suggested as an important causal factor. [9] Panic disorder is associated with major depression, [10] social phobia, generalised anxiety disorder, obsessive compulsive disorder, [11] and a substantial risk of drug and alcohol misuse. [12] It is also associated with avoidant, histrionic, and dependent personality disorders. [11]

PROGNOSIS

The severity of symptoms in people with panic disorder fluctuates considerably, and people commonly have periods of no attacks, or only mild attacks with few symptoms. There is often a long delay between the initial onset of symptoms and presentation for treatment. Recurrent attacks may continue for several years, especially if associated with agoraphobia. Reduced social or occupa-

tional functioning varies among people with panic disorder, and is worse in people with associated agoraphobia. Panic disorder is also associated with an increased rate of attempted suicide, with one study finding that it occurred in 20% of people with panic disorder, compared with 12% of people with panic attacks alone, 6% of those with other psychiatric disorder, and 1% of those with no disorders. The odds ratio for attempted suicide was increased if there were co-morbid conditions. [13] One study analysing data from RCTs and systematic reviews found that co-existence of anxiety and depressive features adversely affected treatment response at 12 years compared with treatment of panic disorder alone. [14]

AIMS OF INTERVENTION To reduce the severity and frequency of panic attacks, phobic avoidance, and anticipatory anxiety; to improve social and occupational functioning, with minimal adverse effects of treatment.

OUTCOMES **Symptom severity** measures of panic attacks, agoraphobia, and associated disability (self-reported and clinician-rated, before and after treatment, and longer term) using general or specific scales for panic disorder (e.g., the Panic and Agoraphobia Scale, the Mobility Inventory for Agoraphobia), relapse rates; **quality of life**; and **adverse effects**.

METHODS *Clinical Evidence* search and appraisal June 2007. The following databases were used to identify studies for this systematic review: Medline 1966 to June 2007, Embase 1980 to June 2007, and The Cochrane Database of Systematic Reviews and Cochrane Central Register of Controlled Clinical Trials 2007, Issue 2. Additional searches were carried out using these websites: NHS Centre for Reviews and Dissemination (CRD) — for Database of Abstracts of Reviews of Effects (DARE) and Health Technology Assessment (HTA), Turning Research into Practice (TRIP), and NICE. We also searched for retractions of studies included in the review. Abstracts of the studies retrieved from the initial search were assessed by an information specialist. Selected studies were then sent to the author for additional assessment, using pre-determined criteria to identify relevant studies. Study design criteria for assessment in this review were: published systematic reviews and RCTs in any language, at least single blinded, and containing more than 20 people of whom more than 80% were followed up for a minimum of 6 months. We excluded all studies described as "open", "open label", or not blinded unless blinding was not possible. In addition, we use a regular surveillance protocol to capture harms alerts from organisations such as the FDA and the UK Medicines and Healthcare products Regulatory Agency (MHRA), which are added to the reviews as required. This review includes RCTs in people aged 18 to 65 years old, and excludes RCTs in people solely with the co-morbidity of head injury and organic brain disorder, or people solely with phobic avoidance of social phobia (i.e., social phobia without panic disorder). To aid readability of the numerical data in our reviews, we round many percentages to the nearest whole number. Readers should be aware of this when relating percentages to summary statistics such as RRs and ORs. We have performed a GRADE evaluation of the quality of evidence for interventions included in this review (see table, p 62). The categorisation of the quality of the evidence (high, moderate, low, or very low) reflects the quality of evidence available for our chosen outcomes in our defined populations of interest. These categorisations are not necessarily a reflection of the overall methodological quality of any individual study, because the Clinical Evidence population and outcome of choice may represent only a small subset of the total outcomes reported, and population included, in any individual trial. For further details of how we perform the GRADE evaluation and the scoring system we use, please see our website (www.clinicalevidence.com).

QUESTION What are the effects of non-drug treatments for panic disorder?

OPTION CBT VERSUS NO TREATMENT

- For GRADE evaluation of interventions for Panic disorder, see table, p 62 .
- CBT is effective in reducing symptoms of panic disorder over 6 months or longer, but we don't know whether it is more effective than other psychological treatments.
- CBT is more effective than waiting list and other controls in reducing symptoms in panic disorder with or without mild to moderate agoraphobia.

Benefits and harms

CBT versus placebo or no treatment:

We found five systematic reviews. [15] [16] [17] [18] [19] The first and second systematic reviews [15] [16] were included in the third and fourth systematic reviews so are not reported further. Two other reviews performed different meta-analyses so are reported below. [17] [18] A fifth review included additional RCTs but did not perform a meta-analysis

so results from those RCTs meeting *Clinical Evidence* inclusion criteria are reported below. For full details of review methods and inclusion criteria, see further information about studies. [19]

Symptom severity

CBT or behavioural therapy compared with placebo or no treatment CBT or behavioural therapy may be more effective at improving anxiety and clinical significance scores, but we don't know whether they are more effective at improving depression scores. We don't know whether CBT with or without exposure to the panic-inducing stimulus is more effective than placebo or waiting list control at improving symptoms in people with panic disorder and severe agoraphobia (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Global symptoms					
[17] Systematic review	People with panic disorder with and without agoraphobia Number of people and RCTs in analysis not specified	**Treatment effect** with cognitive behavioural treatments in general with control (not specified) Absolute results not reported	Effect size 0.68 (see further information on studies for details on effect size) Significance not reported		
[20] RCT **4-armed trial**	186 people with panic disorder In review [19] The RCT compared CBT versus brief CBT versus brief CBT plus computer programme versus waiting list	**Proportion of people who were panic free at follow-up , 6 months** 66% with CBT (12 sessions) 65% with brief CBT (6 sessions) 63% with brief CBT plus computer programme 9% with waiting list Absolute numbers not reported Treatment was given for 12 weeks followed by 6 months' follow-up	P >0.05 (among group comparison)		
[21] RCT **3-armed trial**	97 people with panic disorder with or without agoraphobia in primary care In review [19] The RCT compared individual CBT versus group CBT versus waiting list	**Proportion of follow-up attenders who completed follow-up without receiving intervening treatment , 6 months** 20/37 (54%) with individual CBT 12/38 (31%) with group CBT 0/22 (0%) with waiting list Treatment was given for 3 months followed by 3 months' follow-up	Significance not assessed		
[22] RCT	67 people with panic disorder with or without agoraphobia In review [19]	**Proportion of people who were panic free at follow-up , 6 months** 83% with group CBT (including education, breathing retraining plus interoceptive exposure) 30% with waiting list Absolute numbers not reported Treatment was given for 8 weeks' treatment followed by 6 months' follow-up	P value not reported		
[23] RCT **3-armed trial**	36 people with panic disorder In review [19] The third arm assessed the effects	**Proportion of people with 'clinical improvement' in frequency of panic attacks (criteria not reported) , end of treatment** 83% with group CBT	P <0.01 (group CBT *v* waiting list control)	○○○	CBT

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
	of bibliotherapy CBT	25% with waiting list Absolute numbers not reported Treatment was given for 8 weeks followed by 6 months' follow-up			
[24] RCT **3-armed trial**	45 people with DSM-IV-diagnosed panic disorder with or without agoraphobia In review [18] [19] The third arm assessed the effects of CBT plus breathing retraining	**Proportion of people with high end-state function (defined as panic frequency = 0, anxiety on Sheehan Patient-Rated Anxiety Scale <30, and phobic avoidance on the Mobility Inventory Scale <1.5) , end of treatment** 38% with CBT (12 sessions over 12 weeks) 0% with control (delayed treatment) Absolute numbers not reported	P <0.0001 (CBT *v* control)	○○○	CBT
Anxiety					
[18] Systematic review	People with panic disorder with or without agoraphobia Number of people and RCTs in analysis not specified	**Anxiety** with CBT or behavioural therapy with no treatment Absolute results not reported	Effect size +0.87 95% CI +0.71 to +1.03 Positive value for effect size means first intervention more effective than comparator; larger value means greater effect The review did not report details of method of randomisation Results should be interpreted with caution (see further information on studies for more details)	○○○	CBT
[18] Systematic review	People with panic disorder with or without agoraphobia Number of people and RCTs in analysis not specified	**Anxiety** with CBT or behavioural therapy with pill placebo Absolute results not reported	Effect size +0.51 95% CI +0.30 to +0.72 Positive value for effect size means first intervention more effective than comparator; larger value means greater effect The review did not report details of method of randomisation Results should be interpreted with caution (see further information on studies for more details)	○○○	CBT
[25] RCT	231 alcoholic inpatients with panic disorder In review [19]	**Anxiety , 12 months** with Group CBT plus standard alcohol treatment programme (4 weeks) with standard alcohol treatment programme alone Absolute results reported graphically	Reported as not significant P value not reported Outcome improved from baseline in both groups	⟷	Not significant
Depression/mood					
[18] Systematic review	People with panic disorder with or without agoraphobia Number of people and RCTs in analysis not specified	**Depression** with CBT or behavioural therapy with no treatment Absolute results not reported	Effect size +0.72 95% CI +0.54 to +0.90 Positive value for effect size means first intervention more effective than comparator; larger value means greater effect The review did not report details of method of randomisation	○○○	CBT

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
			Results should be interpreted with caution (see further information on studies for more details)		
[18] Systematic review	People with panic disorder with or without agoraphobia Number of people and RCTs in analysis not specified	**Depression** with CBT or behavioural therapy with pill placebo Absolute results not reported	Effect size +0.27 95% CI –0.02 to +0.56 Positive value for effect size means first intervention more effective than comparator; larger value means greater effect The review did not report details of method of randomisation Results should be interpreted with caution (see further information on studies for more details)	⟷	Not significant
[25] RCT	231 alcoholic inpatients with panic disorder In review [19]	**Mood , 12 months** with Group CBT plus standard alcohol treatment programme (4 weeks) with standard alcohol treatment programme alone Absolute results reported graphically	Reported as not significant P value not reported Outcome improved from baseline in both groups	⟷	Not significant
'Clinically significant improvement'					
[18] Systematic review	People with panic disorder with or without agoraphobia Number of people and RCTs in analysis not specified	**Clinically significant improvement (not further defined)** with CBT or behavioural therapy with no treatment Absolute results not reported	Effect size +1.36 95% CI +1.10 to +1.62 Positive value for effect size means first intervention more effective than comparator; larger value means greater effect The review did not report details of method of randomisation Results should be interpreted with caution (see further information on studies for more details)	○○○	CBT
[18] Systematic review	People with panic disorder with or without agoraphobia Number of people and RCTs in analysis not specified	**Clinically significant improvement (not further defined)** with CBT or behavioural therapy with pill placebo Absolute results not reported	Effect size +0.58 95% CI +0.25 to +0.92 Positive value for effect size means first intervention more effective than comparator; larger value means greater effect The review did not report details of method of randomisation Results should be interpreted with caution (see further information on studies for more details)	○○○	CBT

Quality of life

CBT or behavioural therapy compared with placebo or no treatment We don't know whether CBT or behavioural therapy are more effective at improving quality-of-life scores (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Quality of life					
[18] Systematic review	People with panic disorder with or without agoraphobia Number of people and RCTs in analysis not specified	**Quality of life** with CBT or behavioural therapy with no treatment Absolute results not reported	Effect size +0.85 95% CI +0.48 to +1.21 Positive value for effect size means first intervention more effective than comparator; larger value means greater effect The review did not report details of method of randomisation Results should be interpreted with caution (see further information on studies for more details)	○○○	CBT
[18] Systematic review	People with panic disorder with or without agoraphobia Number of people and RCTs in analysis not specified	**Clinically significant improvement (not further defined)** with CBT or behavioural therapy with pill placebo Absolute results not reported	Effect size +0.42 95% CI –0.11 to +0.94 Positive value for effect size means first intervention more effective than comparator; larger value means greater effect The review did not report details of method of randomisation Results should be interpreted with caution (see further information on studies for more details)	⟷	Not significant

No data from the following reference on this outcome. [15] [16] [17] [19]

Adverse effects

No data from the following reference on this outcome. [15] [16] [17] [18] [19]

Further information on studies

[17] The review (search date 2004) included several meta-analyses of CBT for the treatment of different anxiety disorders and depressive disorder. The authors recalculated effect sizes for treatments from these meta-analyses, with an adjustment to account for different control-group response rates, to enable a comparison of different treatments where direct-comparison studies had not been performed. The review reported than an effect size of 1.0 would represent a large treatment effect (indicating that the average person in one group would have an outcome superior to that of 84% of people in the control group), while an effect size of 0.0 would indicate no treatment effect.

[18] The review (search date 2002) [18] identified nine meta-analyses, and included a total of 124 controlled clinical studies of CBT or behavioural therapy, pharmacotherapy, or behavioural therapy plus pharmacotherapy in people with panic disorder, agoraphobia, or panic disorder plus agoraphobia; the review identified 32 controlled clinical studies comparing CBT or behavioural therapy versus no treatment, and 13 controlled studies comparing CBT or behavioural therapy versus placebo. Inclusion criteria of the review were a minimum of four people, and a waiting list, pill placebo, or therapy placebo group: the review did not specify that studies had to be randomised. The review calculated effect sizes to determine the additional benefit from active treatment compared with control. [18] The review found no evidence of publication bias in studies that had compared CBT versus waiting list, placebo, behavioural therapy, or combination treatment. However, these results should be interpreted with caution since response rates tend to be greater in pill placebo control groups as opposed to waiting list control groups, and because few studies of CBT used an intention-to-treat analysis.

[19] This review (search date 2005) identified 298 controlled clinical studies of treatments for panic disorder, but did not perform a meta-analysis. The review identified 30 controlled clinical randomised and non-randomised studies of CBT compared with waiting list or placebo control, including 13 that were also identified by the third review, [18] and five that were not included in any of the other reviews and that met our inclusion criteria. It graded evidence, and defined grade 1 evidence as: the conclusion being supported by at least two studies with a high level of proof or good systematic review; and grade 2 evidence as: the conclusion being supported by one study with a high level of proof and at least two studies with a medium level of proof. The authors of the review concluded from included studies that there was good evidence of benefit from CBT, with or without exposure to the panic-inducing stimulus, in people with panic disorder without agoraphobia or mild to moderate agoraphobia (evidence grade 1), but that the role of CBT in the treatment of panic disorder with severe agoraphobia was not established.

Comment: None.

OPTION CBT VERSUS DRUG TREATMENTS

- For GRADE evaluation of interventions for Panic disorder, see table, p 62 .
- We don't know whether CBT alone is more effective than antidepressants alone, but weak evidence suggests that the effects of CBT may last longer.
- Combined treatment with CBT plus antidepressants has been shown to be more effective than CBT alone or antidepressants alone in reducing symptoms in the short term.

Benefits and harms

CBT versus antidepressants:

We found three systematic reviews. [18] [17] [19] Two of the reviews performed different meta-analyses so both are reported here. [18] [17] The third review did not perform a meta-analysis and identified no RCTs that met *Clinical Evidence* inclusion criteria so is not reported further. [19] For full details of the inclusion criteria of the reviews, see further information about studies.

Symptom severity

CBT or cognitive therapy compared with antidepressants We don't know whether CBT or cognitive therapy is more effective than pharmacotherapy (mainly SSRIs and tricyclic antidepressants but also including benzodiazepines) at improving symptoms in people with panic disorder (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Global symptoms					
[17] Systematic review	People with panic disorder with and without agoraphobia Number of people and RCTs in analysis not specified	**Treatment effect** Effect size 0.68 with cognitive behavioural treatments in general Effect size 0.47 with drug treatments (not further defined in review) The review did not define "drug treatments" See further information on studies for details on effect size	Significance not reported Analyses based on indirect comparisons, and so should be interpreted with extreme caution		
[17] Systematic review	People with panic disorder with and without agoraphobia Number of people and RCTs in analysis not specified	**"Slippage" in effect size , 1 year** –0.07 with cognitive behavioural treatments in general –0.46 with drug treatments (not further defined in review) The review did not define "drug treatments"	Significance not reported Analyses based on indirect comparisons, and so should be interpreted with extreme caution		

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		See further information on studies for details on effect size			
Anxiety					
[18] Systematic review	People with panic disorder with or without agoraphobia Number of people and RCTs in analysis not specified	**Anxiety** with drug treatments with CBT or behavioural therapy Absolute results not reported	Eeffect size +0.27 95% CI –0.07 to +0.62 Positive value for effect size means first intervention more effective than comparator; larger value means greater effect The review did not report details of method of randomisation The review found evidence of publication bias (see further information on studies for more details)	⟷	Not significant
Depression					
[18] Systematic review	People with panic disorder with or without agoraphobia Number of people and RCTs in analysis not specified	**Depression** with drug treatments with CBT or behavioural therapy Absolute results not reported	Effect size +0.21 95% CI –0.34 to +0.75 Positive value for effect size means first intervention more effective than comparator; larger value means greater effect The review did not report details of method of randomisation The review found evidence of publication bias (see further information on studies for more details)	⟷	Not significant
'Clinical significant improvement'					
[18] Systematic review	People with panic disorder with or without agoraphobia Number of people and RCTs in analysis not specified	**Clinically significant improvement (not further defined)** with drug treatments with CBT or behavioural therapy Absolute results not reported	Effect size +0.09 95% CI –0.38 to +0.56 Positive value for effect size means first intervention more effective than comparator; larger value means greater effect The review did not report details of method of randomisation The review found evidence of publication bias (see further information on studies for more details)	⟷	Not significant

Quality of life

No data from the following reference on this outcome. [17] [18] [19]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Withdrawal rate					
[18] Systematic review	People with panic disorder with or without agoraphobia Number of people and RCTs in analysis not specified	**Average withdrawal rates** 21% with drug treatments 16% with CBT or behavioural therapy Absolute numbers not reported A total of 11% of people withdrew because of drug-related adverse effects; rates were comparable for SSRIs (23%), tricyclic antidepressants (24%), and benzodiazepines (18%)	Significance not assessed The review did not report details of method of randomisation The review found evidence of publication bias (see further information on studies for more details)		

No data from the following reference on this outcome. [17] [19]

CBT plus buspirone versus CBT alone:
See option on buspirone, p 49 .

Further information on studies

[17] The review (search date 2004) included several meta-analyses and recalculated effect sizes for treatments from these meta-analyses, with an adjustment to account for different control-group response rates, to enable a comparison of different treatments where direct-comparison studies had not been performed. The review reported than an effect size of 1.0 would represent a large treatment effect (indicating that the average person in one group would have an outcome superior to that of 84% of people in the control group), while an effect size of 0.0 would indicate no treatment effect.

[18] The review (search date 2002) identified 11 controlled clinical studies directly comparing cognitive therapy or CBT versus pharmacotherapy in people with panic disorder, agoraphobia, or panic disorder plus agoraphobia. [18] Inclusion criteria of the review were a minimum of four people, and a waiting list, pill placebo, or therapy placebo group: review did not specify that studies had to be randomised. Drug classes investigated were mainly SSRIs and tricyclic antidepressants, but benzodiazepines were also included. Effect sizes were calculated to determine the additional benefit from active treatment compared with control. The review found some evidence of publication bias in studies comparing CBT versus drug treatments. The author adjusted the calculated effect sizes to account for publication bias, and found that this increased the effect size for CBT or behavioural therapy compared with drug treatment (P <0.01).

[19] The review (search date 2005) identified 10 controlled clinical studies, of which four were included in the first review. None of the other studies met our inclusion criteria. The review did not pool data, but graded evidence based on included studies. It graded evidence, and defined grade 1 evidence as: the conclusion being supported by at least two studies with a high level of proof or good systematic review; and grade 2 evidence as: the conclusion being supported by one study with a high level of proof and at least two studies with a medium level of proof. The review concluded that the effect of psychotherapy was longer lasting compared with that of drug treatments (reported as grade 2 evidence [defined as the conclusion being supported by one study with a high level of proof and at least two studies with a medium level of proof]); review is not discussed further.

Comment: None.

OPTION CBT VERSUS OTHER PSYCHOLOGICAL TREATMENTS

- For GRADE evaluation of interventions for Panic disorder, see table, p 62 .

- Self-help using CBT techniques and therapist-based CBT may be equally effective at improving symptoms of panic disorder.

Benefits and harms

CBT versus behavioural therapy:

We found two systematic reviews. [18] [19] For full details of the methods and inclusion crteria of the first review, [18] see further information about studies. The second review (search date 2005) did not perform a meta-analysis. [19] It identified seven controlled trials, of which three were also identified by the first review. [18] None of the other trial met our inclusion criteria, and so no data from this review [19] are reported below.

Symptom severity

CBT compared with behavioural therapy CBT may be more effective at improving depression scores, but not anxiety scores or clinical significance scores (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Anxiety					
[18] Systematic review	People with panic disorder with or without agoraphobia Number of people and RCTs in analysis not specified	**Anxiety** with CBT with behavioural therapy Absolute results not reported	Effect size +0.09 (CBT *v* behavioural therapy) 95% CI –0.07 to +0.24 Positive value for effect size means first intervention more effective than comparator; larger value means greater effect The review did not report details of method of randomisation	⟷	Not significant
Depression					
[18] Systematic review	People with panic disorder with or without agoraphobia Number of people and RCTs in analysis not specified	**Depression** with CBT with behavioural therapy Absolute results not reported	Effect size +0.18 (CBT *v* behavioural therapy) 95% CI +0.01 to +0.35 Positive value for effect size means first intervention more effective than comparator; larger value means greater effect The review did not report details of method of randomisation	○○○	CBT
'Clinically significant improvement'					
[18] Systematic review	People with panic disorder with or without agoraphobia Number of people and RCTs in analysis not specified	**Clinically significant improvement (not further defined)** with CBT with behavioural therapy Absolute results not reported	Effect size +0.13 (CBT *v* behavioural therapy) 95% CI –0.13 to +0.39 Positive value for effect size means first intervention more effective than comparator; larger value means greater effect The review did not report details of method of randomisation	⟷	Not significant

Quality of life

CBT compared with behavioural therapy We don't know whether CBT is more effective at improving quality of life (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Quality of life					
[18] Systematic review	People with panic disorder with or without agoraphobia Number of people and RCTs in analysis not specified	**Quality of life** with CBT with behavioural therapy Absolute results not reported	Effect size –0.11 (CBT *v* behavioural therapy) 95% CI –0.63 to +0.42 Positive value for effect size means first intervention more effective than comparator; larger value means greater effect The review did not report details of method of randomisation	⟷	Not significant

Adverse effects

No data from the following reference on this outcome. [18]

CBT versus exposure:
We found one RCT. [26]

Symptom severity

CBT compared with exposure We don't know whether CBT is more effective than exposure *in vivo* at improving symptoms (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Global symptoms					
[26] RCT **3-armed trial**	73 people with DSM-IV diagnosis of panic with agoraphobia The third arm assessed the effects of waiting list control (16 weeks; see further information on studies)	**Behavioural assessor ratings** with CBT with exposure *in vivo* Absolute results not reported Both active treatment groups received 12 to 16 weekly individual sessions	Reported as not significant (CBT *v* exposure *in vivo*) P value not reported Complex analysis using analysis of variance (ANOVA)	⟷	Not significant
[26] RCT **3-armed trial**	73 people with DSM-IV diagnosis of panic with agoraphobia The third arm assessed the effects of waiting list control (16 weeks; see further information on studies)	**Behavioural approach tests** with CBT with exposure *in vivo* Absolute results not reported Both active treatment groups received 12 to 16 weekly individual sessions	Reported as not significant (CBT *v* exposure *in vivo*) P value not reported Complex analysis using analysis of variance (ANOVA)	⟷	Not significant
[26] RCT **3-armed trial**	73 people with DSM-IV diagnosis of panic with agoraphobia The third arm assessed the effects of waiting list control (16 weeks; see	**Self-monitoring of panic attacks** with CBT with exposure *in vivo* Absolute results not reported Both active treatment groups received 12 to 16 weekly individual sessions	Reported as not significant (CBT *v* exposure *in vivo*) P value not reported Complex analysis using analysis of variance (ANOVA)	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
	further information on studies)				
[26] RCT **3-armed trial**	73 people with DSM-IV diagnosis of panic with agoraphobia The third arm assessed the effects of waiting list control (16 weeks; see further information on studies)	**Self-report scales of agoraphobia and panic** with CBT with exposure *in vivo* Absolute results not reported Both active treatment groups received 12 to 16 weekly individual sessions	Reported as not significant (CBT *v* exposure *in vivo*) P value not reported Complex analysis using analysis of variance (ANOVA)	⟷	Not significant
'Clinically significant improvement'					
[26] RCT **3-armed trial**	73 people with DSM-IV diagnosis of panic with agoraphobia The third arm assessed the effects of waiting list control (16 weeks; see further information on studies)	**Proportion of people with a clinically significant improvement (based on ratings of phobic severity, agoraphobia score, and diagnosis criteria), post-treatment** 79% with CBT 67% with exposure *in vivo* Absolute numbers not reported Both active treatment groups received 12 to 16 weekly individual sessions	Reported as not significant (CBT *v* exposure *in vivo*) P value not reported	⟷	Not significant
[26] RCT **3-armed trial**	73 people with DSM-IV diagnosis of panic with agoraphobia The third arm assessed the effects of waiting list control (16 weeks; see further information on studies)	**Proportion of people with a clinically significant improvement (based on ratings of phobic severity, agoraphobia score, and diagnosis criteria), 1 year** 76% with CBT 74% with exposure *in vivo* Absolute numbers not reported Both active treatment groups received 12 to 16 weekly individual sessions	Reported as not significant (CBT *v* exposure *in vivo*) P value not reported	⟷	Not significant

Quality of life

No data from the following reference on this outcome. [26]

Adverse effects

No data from the following reference on this outcome. [26]

CBT versus applied relaxation:

See option on applied relaxation, p 14 .

CBT versus breathing retraining:
See option on breathing retraining, p 32 .

CBT versus self-help methods:
See option on self-help, p 28 .

Further information on studies

[18] The review (search date 2002) identified 26 controlled studies comparing CBT versus behavioural therapy in people with panic disorder, agoraphobia, or panic disorder plus agoraphobia, with a minimum of four people, including a waiting list, pill placebo, or therapy placebo group. Effect sizes were calculated to determine the additional benefit from active treatment compared with control. The review specified that trials had to have a control group (waiting list, pill placebo, or therapy placebo) but did not specify that they had to be randomised

[26] For the analysis of active treatment versus waiting list control, the RCT combined results from both the CBT and exposure groups together and so we have not reported these results further.

Comment: None.

OPTION APPLIED RELAXATION

- For GRADE evaluation of interventions for Panic disorder, see table, p 62 .
- Applied relaxation is likely to be effective in reducing symptoms.

Benefits and harms

Applied relaxation versus waiting list control:

We found two systematic reviews. [18] [19] The reviews identified the same two RCTs comparing applied relaxation versus waiting lost control. [28] [29] Neither review analysed the results of these RCTs separately from those of other psychological treatments so we report the results regarding applied relaxation from the RCTs separately here.

Symptom severity

Applied relaxation compared with waiting list control Applied relaxation may be more effective at improving panic and anxiety symptoms at 10 to 12 weeks, but we don't know whether it is more effective at increasing the proportion of people who are panic free at 10 weeks (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Frequency of panic attack					
[28] RCT **3-armed trial**	64 people with DSM-III criteria for panic disorder with moderate or mild agoraphobia, 9 without avoidance In review [18] [19] The third arm assessed the effects of CBT There were significant differences between groups at baseline with regard to panic fre-	**Number of panic attacks , 10 weeks** with applied relaxation with minimal contact control Absolute results not reported Active treatment took place over 10 sessions once a week	Reported as significant (applied relaxation *v* minimal contact control) P value not reported	○○○	applied relaxation

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
	quency and symptom severity (P values not reported)				
Freedom from panic attacks					
[28] RCT **3-armed trial**	64 people with DSM-III criteria for panic disorder with moderate or mild agoraphobia, 9 without avoidance In review [18] [19] There were significant differences between groups at baseline with regard to panic frequency and symptom severity (P values not reported)	**Proportion of people who were panic free , 10 weeks** 9/19 (47%) with applied relaxation 11/17 (65%) with CBT 8/22 (36%) with minimal contact control Active treatment took place over 10 sessions once a week	P >0.05 (among-group comparison)		
Global symptoms					
[28] RCT **3-armed trial**	64 people with DSM-III criteria for panic disorder with moderate or mild agoraphobia, 9 without avoidance In review [18] [19] The third arm assessed the effects of CBT There were significant differences between groups at baseline with regard to panic frequency and symptom severity (P values not reported)	**Global function (measured by Anxiety Disorders Interview Schedule and Hamilton Anxiety and Depression scales) , 10 weeks** with applied relaxation with minimal contact control Absolute results not reported Active treatment took place over 10 sessions once a week	Reported as significant (applied relaxation *v* minimal contact control) P value not reported	○○○	applied relaxation
[28] RCT **3-armed trial**	64 people with DSM-III criteria for panic disorder with moderate or mild agoraphobia, 9 without avoidance In review [18] [19] There were significant differences between groups at baseline with regard to panic frequency and symptom severity (P values not reported)	**Panic symptoms , 6 months** with applied relaxation with CBT with minimal contact control Absolute results not reported Active treatment took place over 10 sessions once a week	Reported as not significant (among-group comparison) P value not reported	⟷	Not significant
[29] RCT **4-armed trial**	64 people In review [18] [19] The third and fourth arms assessed the effects	**Improvement in a composite panic/anxiety outcome (consisting of 17 validated panic and anxiety measures) , 12 weeks** From +1.12 to –0.01 with applied relaxation	P <0.05 (applied relaxation *v* waiting list control)	○○○	applied relaxation

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
	of CBT and imipramine	From 1.22 to 0.94 with waiting list control 32 people in this analysis (16 people in each group)			
Depression					
[29] RCT **4-armed trial**	64 people In review [18] [19] The third and fourth arms assessed the effects of CBT and imipramine	**Improvement in depression (measured by Beck Depression Inventory; scale 0 to 63, change from baseline) , 12 weeks** From 18.6 to 9.8 with applied relaxation From 21.3 to 20.9 with waiting list control 32 people in this analysis (16 people in each group)	Reported as significant (applied relaxation *v* waiting list control) P value not reported	○○○	applied relaxation

Quality of life

No data from the following reference on this outcome. [28] [29]

Adverse effects

No data from the following reference on this outcome. [28] [29]

Applied relaxation versus CBT:

We found two systematic reviews. [18] [19] The reviews identified five RCTs comparing applied relaxation versus CBT. [28] [29] [30] [31] [32] Neither review analysed the effects of applied relaxation separately from those of other psychological treatments so we report the results of the individual RCTs below.

Symptom severity

Applied relaxation compared with CBT We don't know whether applied relaxation is more effective at improving symptoms (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Frequency of panic attack					
[30] RCT **3-armed trial**	36 people with panic disorder and with no or mild agoraphobia In review [18] [19] The third arm assessed the effects of a waiting list control (18 people); people were selected for control group after the initial group enrolled had been ran-	**Panic frequency , 12 weeks** with applied relaxation with CBT Absolute results not reported	P = 0.01 (applied relaxation *v* CBT)	○○○	CBT

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
	domised to applied relaxation or CBT				
[30] RCT **3-armed trial**	36 people with panic disorder and with no or mild agoraphobia In review [18] [19] The third arm assessed the effects of a waiting list control (18 people); people were selected for control group after the initial group enrolled had been randomised to applied relaxation or CBT	**Panic frequency , 6 months** with applied relaxation with CBT Absolute results not reported	P <0.00035 (applied relaxation *v* CBT)	○○○	CBT
Freedom from panic attacks					
[28] RCT **3-armed trial**	64 people with DSM-III criteria for panic disorder with moderate or mild agoraphobia, 9 without avoidance In review [18] [19] There were significant differences between groups at baseline with regard to panic frequency and symptom severity (P values not reported)	**Proportion of people who were panic free , 10 weeks** 9/19 (47%) with applied relaxation 11/17 (65%) with CBT 8/22 (36%) with minimal contact control Active treatment took place over 10 sessions once a week	P >0.05 (among-group comparison)	⟷	Not significant
[30] RCT **3-armed trial**	36 people with panic disorder and with no or mild agoraphobia In review [18] [19] The third arm assessed the effects of a waiting list control (18 people); people were selected for control group after the initial group enrolled had been randomised to applied relaxation or CBT	**Proportion of people who were panic free , 4 weeks** with applied relaxation with CBT Absolute results not reported	P = 0.04 (applied relaxation *v* CBT)	○○○	CBT
[30] RCT **3-armed trial**	36 people with panic disorder and with no or mild agoraphobia In review [18] [19] The third arm assessed the effects of a waiting list control (18 people); people were selected for control group after the initial group enrolled had been ran-	**Proportion of people who were panic free , 6 months** with applied relaxation with CBT Absolute results not reported	P = 0.04 (applied relaxation *v* CBT)	○○○	CBT

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
	domised to applied relaxation or CBT				
Global symptoms					
[32] RCT	38 people with DSM-III criteria for panic disorder with no or mild avoidance In review [18] [19]	**Independent assessor ratings , 1 year** with applied relaxation with CBT Absolute results not reported Treatments were given over 12 sessions once a week The RCT found that applied relaxation and CBT both significantly improved various outcomes at 12 weeks compared with baseline measurements	Reported as no significant difference between groups P value not reported	⟷	Not significant
[32] RCT	38 people with DSM-III criteria for panic disorder with no or mild avoidance In review [18] [19]	**Self-report scales , 1 year** with applied relaxation with CBT Absolute results not reported Treatments were given over 12 sessions once a week The RCT found that applied relaxation and CBT significantly improved various outcomes at 12 weeks compared with baseline measurements	Reported as no significant difference between groups P value not reported	⟷	Not significant
[32] RCT	38 people with DSM-III criteria for panic disorder with no or mild avoidance In review [18] [19]	**Self-observation of panic attacks , 1 year** with applied relaxation with CBT Absolute results not reported Treatments were given over 12 sessions once a week The RCT found that applied relaxation and CBT significantly improved various outcomes at 12 weeks compared with baseline measurements	Reported as no significant difference between groups P value not reported	⟷	Not significant
[31] RCT **3-armed trial**	45 people with DSM-III criteria for panic disorder with agoraphobia In review [18] [19] The third arm assessed the effects of exposure *in vivo*	**Mean score on the therapist-assessed Behavioural Agoraphobia Test , post-treatment** with applied relaxation with CBT Absolute results reported graphically All treatments were given over 12 sessions once a week The RCT found that all three treatments significantly improved agoraphobia self-report measures at 12 weeks compared with baseline measures (P <0.0001)	P <0.05 (applied relaxation *v* CBT) All groups had self-exposure instructions: these have been shown to be independently effective in the treatment of agoraphobia, which makes interpretation of the results difficult	○○○	applied relaxation
[31] RCT **3-armed trial**	45 people with DSM-III criteria for panic disorder with agoraphobia	**Mean score on the therapist-assessed Behavioural Agoraphobia Test , 1 year**	Reported as not significant (applied relaxation *v* CBT) All groups had self-exposure instructions: these have been	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
	In review [18] [19] The third arm assessed the effects of exposure *in vivo*	with applied relaxation with CBT Absolute results reported graphically All treatments were given over 12 sessions once a week	shown to be independently effective in the treatment of agoraphobia, which makes interpretation of the results difficult		
[29] RCT **4-armed trial**	64 people In review [18] [19] The third and fourth arms assessed the effects of imipramine and waiting list control	**Improvement in a composite panic/anxiety outcome (consisting of 17 validated panic and anxiety measures) , 12 weeks** From +1.06 to +0.02 with applied relaxation From +0.83 to –0.82 with CBT 32 people in this analysis (16 people in each group)	Reported as significant (applied relaxation *v* CBT) P value not reported	○○○	CBT

Quality of life

No data from the following reference on this outcome. [28] [29] [30] [31] [32]

Adverse effects

No data from the following reference on this outcome. [28] [29] [30] [31] [32]

Applied relaxation versus drug treatments:

We found two systematic reviews. [18] [19] The reviews identified one RCT comparing applied relaxation versus drug treatments. [29] The reviews did not analyse the results of this RCT separately from those of other psychological treatments. [18] [19] The second review [19] identified 10 controlled studies, six of which were included in the first review, including the RCT reported here. [29] Again, the review did not discuss the benefits of applied relaxation separately from other psychological treatments.

Symptom severity

Applied relaxation compared with imipramine Applied relaxation may be less effective at improving symptoms (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Global symptoms					
[29] RCT **4-armed trial**	64 people In review [18] [19] The third and fourth arms assessed the effects of CBT and waiting list control	**Improvement in a composite panic/anxiety outcome (consisting of 17 validated panic and anxiety measures) , 12 weeks** From 1.06 to 0.02 with applied relaxation From 1.15 to 0.01 with imipramine 32 people in this analysis (16 people in each group)	Reported as not significant (applied relaxation *v* imipramine) P value not reported	⟷	Not significant

Quality of life

No data from the following reference on this outcome. [29]

Adverse effects

No data from the following reference on this outcome. [29]

Applied relaxation versus panic focused psychodynamic psychotherapy:
See option on brief dynamic psychotherapy, p 34 .

Further information on studies

Comment: One RCT found that cognitive measures taken at the end of treatment were significant predictors of outcome at follow-up. [29]

OPTION CLIENT-CENTRED THERAPY

- For GRADE evaluation of interventions for Panic disorder, see table, p 62 .
- Client-centred therapy is likely to be effective in reducing symptoms.
- We found no direct evidence from RCTs about whether client-centred therapy is better than no active treatment.

Benefits and harms

Client-centred therapy versus no treatment:
We found no RCTs comparing client-centred therapy with placebo or no treatment.

Client-centred therapy versus client-centred therapy plus exposure:
We found two systematic reviews, [18] [19] which identified two RCTs. [34] [35] The RCTs assessed people for panic, using a variety of scales, on admission, at discharge (10–14 weeks), and at 3, 6, and 12 months' follow-up. The RCTs found that both client-centred therapy and client-centred therapy plus exposure treatment significantly reduced panic and avoidance symptoms compared with baseline measures (results presented graphically, P value not reported).

Symptom severity

Client-centred therapy compared with client-centred therapy plus exposure We don't know whether client-centred therapy is more effective than client-centred therapy plus additional behavioural exposure treatment at improving symptoms (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Agoraphobia					
[34] RCT	40 people In review [18] [19] The RCT included inpatients with severe panic and agoraphobia, some of whom had been treated by pharmacological means without success	**Agoraphobia symptoms , 3 months** with client-centred therapy plus exposure with client-centred therapy Absolute results reported graphically	Reported as significant P value not reported	○○○	client-centred therapy plus exposure
Anxiety					
[34] RCT	40 people In review [18] [19] The RCT included inpatients with severe panic and agoraphobia, some of whom had been treated by pharmacological means without success	**Anxiety , 12 months** with client-centred therapy plus exposure with client-centred therapy Absolute results reported graphically	Reported as not significant P value not reported	⟷	Not significant
Depression					
[34] RCT	40 people In review [18] [19] The RCT included inpatients with severe panic and agoraphobia, some of whom had been treated by pharmacological means without success	**Depressive symptoms , 12 months** with client-centred therapy plus exposure with client-centred therapy Absolute results reported graphically	Reported as not significant P value not reported	⟷	Not significant
General symptoms					
[34] RCT	40 people In review [18] [19] The RCT included inpatients with severe panic and agoraphobia, some of whom had been treated by pharmacological means without success	**Readiness to expose oneself actively to phobic situations , 6 months** with client-centred therapy plus exposure with client-centred therapy Absolute results reported graphically	Reported as significant P value not reported	○○○	client-centred therapy plus exposure
[35] RCT	68 people In review [18] [19] The RCT used both International ICD-10 and DSM-III-R criteria	**Dependence on the expectations of others** with client-centred therapy plus exposure with client-centred therapy Absolute results reported graphically	Reported as significant P value not reported	○○○	client-centred therapy
[35] RCT	68 people In review [18] [19] The RCT used both International ICD-10 and DSM-III-R criteria	**Level of stress** with client-centred therapy plus exposure with client-centred therapy Absolute results reported graphically	Reported as significant P value not reported	○○○	client-centred therapy

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[35] RCT	68 people In review [18] [19] The RCT used both International ICD-10 and DSM-III-R criteria	**Rate of psychosomatic complaints** with client-centred therapy plus exposure with client-centred therapy Absolute results reported graphically	Reported as significant P value not reported	○○○	client-centred therapy
[35] RCT	68 people In review [18] [19] The RCT used both International ICD-10 and DSM-III-R criteria	**Time taken to feel accepted by social environment** with client-centred therapy plus exposure with client-centred therapy Absolute results reported graphically	Reported as significant P value not reported	○○○	client-centred therapy plus exposure

Quality of life

No data from the following reference on this outcome. [18] [19] [34] [35]

Adverse effects

No data from the following reference on this outcome. [18] [19] [34] [35]

Further information on studies

[34] [35] Both RCTs assessed people for panic, using a variety of scales, on admission, at discharge (10–14 weeks), and at 3, 6, and 12 months' follow-up. The RCTs found that both client-centred therapy and client-centred therapy plus exposure treatment significantly reduced panic and avoidance symptoms compared with baseline measures (results presented graphically, P value not reported).

Comment: None.

OPTION COGNITIVE RESTRUCTURING

- For GRADE evaluation of interventions for Panic disorder, see table, p 62 .
- Cognitive restructuring is likely to be effective in reducing symptoms.
- We found no direct information about whether cognitive restructuring alone is better than no active treatment.

Benefits and harms

Cognitive restructuring versus waiting list or placebo:

We found no systematic review or RCTs comparing cognitive restructuring alone versus placebo or waiting list control.

Cognitive restructuring plus interoceptive exposure compared with waiting list, pill placebo, or psychological placebo:

We found one systematic review comparing cognitive restructuring plus interoceptive exposure versus placebo or no treatment, which included a meta-analysis [16] that was included in, and reanalysed by, a second systematic review. [17] We therefore report only the results from the second review below. [17]

Symptom severity

Cognitive restructuring plus interoceptive exposure compared with waiting list, pill placebo, or psychological placebo

We don't know whether cognitive restructuring plus interoceptive exposure is more effective at improving symptoms (reported as a larger effect size) than waiting list or pill or psychological placebo; review identified did not report on the significance of differences between groups (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Symptom improvement					
[17] Systematic review	People with panic disorder with and without agoraphobia Number of people and RCTs in analysis not specified	**Treatment effect** with cognitive restructuring plus interoceptive exposure with waiting list control Absolute results not reported	Effect size +0.91 (see further information on studies for details on effect size) Significance not reported		
[17] Systematic review	People with panic disorder with and without agoraphobia Number of people and RCTs in analysis not specified	**Treatment effect** with cognitive restructuring plus interoceptive exposure with pill placebo Absolute results not reported	Effect size +0.65 (see further information on studies for details on effect size) Significance not reported		
[17] Systematic review	People with panic disorder with and without agoraphobia Number of people and RCTs in analysis not specified	**Treatment effect** with cognitive restructuring plus interoceptive exposure with psychological placebo Absolute results not reported	Effect size +1.29 (see further information on studies for details on effect size) Significance not reported		

Quality of life

No data from the following reference on this outcome. [17]

Adverse effects

No data from the following reference on this outcome. [17]

Cognitive restructuring versus exposure:

We found three systematic reviews. [17] [18] [19] The first systematic review (search date 2002) [18] identified one RCT [36] but did not analyse the results separately from other psychological treatments so we report the results of the single RCT separately below. The second review (search date 2005) [19] identified one controlled study that was also identified by the first review, [18] but again did not analyse the results separately from other psychological treatments so is not reported further. The third systematic review [17] re-analysed the results of another review; [16] we report the re-analysis below.

Symptom severity

Cognitive restructuring compared with exposure We don't know whether cognitive restructuring is more effective at improving symptoms (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Frequency of panic attacks					
[36] RCT	28 people with DSM-III-R-diagnosed panic disorder with agoraphobia In review [18]	**Frequency of panic attacks** with interoceptive plus exteroceptive exposure therapy with cognitive restructuring Absolute results not reported Active treatments consisted of 15 sessions once a week The RCT found that panic frequency was significantly reduced from 10 weeks in both groups compared with baseline measures (P <0.001); the reduction persisted until post-treatment and at follow-up at 30 weeks	Reported as not significant P value not reported	⟷	Not significant
Global symptoms					
[36] RCT	28 people with DSM-III-R-diagnosed panic disorder with agoraphobia	**Rate of change of behavioural and cognitive variables** with interoceptive plus exteroceptive exposure therapy with cognitive restructuring Absolute results not reported Active treatments consisted of 15 sessions once a week	Reported as not significant P value not reported	⟷	Not significant
[17] Systematic review	People with panic disorder with and without agoraphobia Number of people and RCTs in analysis not specified	**Treatment effect** with cognitive restructuring with situational exposure Absolute results not reported	Effect size –0.95 (see further information on studies for details on effect size) Significance not reported		

Quality of life

No data from the following reference on this outcome. [36] [17]

Adverse effects

No data from the following reference on this outcome. [36] [17]

Further information on studies

[17] The review reported than an effect size of 1.0 would represent a large treatment effect (indicating that the average person in one group would have an outcome superior to that of 84% of people in the control group), while an

effect size of 0.0 would indicate no treatment effect. The review reported effect sizes in favour of cognitive restructuring plus interoceptive exposure, ranging from 0.65 to 1.29 depending on the control group.

Comment: None.

OPTION EXPOSURE (EXTERNAL OR INTEROCEPTIVE)

- For GRADE evaluation of interventions for Panic disorder, see table, p 62 .
- Exposure to the panic-inducing stimulus is likely to be effective in reducing symptoms.

Benefits and harms

Exposure versus control:

We found three systematic reviews [18] [19] [37] and one additional RCT [38] of exposure in the treatment of panic disorder. We excluded the first systematic review because it included non-randomised trials and did not provide methodological details of the studies included in the meta-analysis, making the results difficult to interpret. [37] The second review (search date 2002) [18] included two RCTs of exposure, [34] [39] but did not analyse the results separately from other psychological treatments so we report the results of the individual RCTs below. The third systematic review (search date 2005) [19] identified 12 controlled studies of exposure, two of which were included in the second review, and a further three met our inclusion criteria. This review did not perform a meta-analysis so, again, we report the results of the RCTs that met our inclusion criteria below.

Symptom severity

Exposure compared with control Exposure may be more effective than placebo plus relaxation at increasing the proportion of people who remain well without relapse at 43 weeks. External self-exposure, interoceptive self-exposure, and combined external and interoceptive self-exposure may be more effective than a waiting list control at improving panic and agoraphobia measures (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Proportion of people free from panic attacks					
[22] RCT	67 people with panic disorder with or without agoraphobia In review [19]	**Proportion of people who were panic free at follow-up , 6 months** 83% with group CBT (including education, breathing retraining plus interoceptive exposure) 30% with waiting list Absolute numbers not reported Treatment was given for 8 weeks' treatment followed by 6 months' follow-up	P value not reported		
[38] RCT **4-armed trial**	80 people with panic disorder with agoraphobia In review [19]	**Proportion of people who were panic free , 12 months** with external plus interoceptive self-exposure with external self-exposure with interoceptive self-exposure with control Absolute results not reported Treatments were given for 10 weeks followed by 12 months' follow-up	Reported by review to be not significant (among-group comparison) P value not reported		
[39] RCT	154 people with DSM-III-diagnosed panic disorder with agoraphobia	**Proportion of the people who improved and remained well without relapse , 43 weeks**	P <0.0001 (among-group comparison of results from baseline; no		

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
4-armed trial		36% with exposure (combined treatment) plus alprazolam 29% with relaxation plus alprazolam 62% with exposure (combined treatment) plus placebo 18% with relaxation plus placebo Absolute numbers not reported The dose of alprazolam was high (5 mg/day) Treatments were given for 8 weeks The RCT found that all four treatments significantly improved the proportion of people who were panic free at 8 weeks compared with baseline (see further information on studies for more details and for details on methodological quality of RCT)	between or among group comparisons assessed)		
Panic and agoraphobia					
[38] RCT **4-armed trial**	80 people diagnosed with panic disorder plus agoraphobia In review [19]	**Hamilton Anxiety Scale , 10 weeks** with external self-exposure with interoceptive self-exposure with combined external and interoceptive self-exposure with delayed-treatment control Absolute results reported graphically Treatments were given for 10 weeks People in the delayed-treatment control group were told that their symptoms could improve without treatment and that they would wait for 10 weeks to see if symptoms improved before further intervention	P <0.001 (for all between-group comparisons of individual exposure therapy *v* delayed control)	○○○	exposure therapy
[38] RCT **4-armed trial**	80 people diagnosed with panic disorder plus agoraphobia	**Clinical Global Impression Rating Scale , 10 weeks** with external self-exposure with interoceptive self-exposure with combined external and interoceptive self-exposure with delayed-treatment control Absolute results reported graphically Treatments were given for 10 weeks People in the delayed-treatment control group were told that their symptoms could improve without treatment and that they would wait for 10 weeks to see if symptoms improved before further intervention	P <0.001 (for all between-group comparisons of individual exposure therapy *v* delayed control)	○○○	exposure therapy

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[38] RCT **4-armed trial**	80 people diagnosed with panic disorder plus agoraphobia	**Agoraphobic Cognitions Scale, 10 weeks** with external self-exposure with interoceptive self-exposure with combined external and interoceptive self-exposure with delayed-treatment control Absolute results reported graphically Treatments were given for 10 weeks People in the delayed-treatment control group were told that their symptoms could improve without treatment and that they would wait for 10 weeks to see if symptoms improved before further intervention	P <0.001 (for all between-group comparisons of individual exposure therapy *v* delayed control)	○○○	exposure therapy

Quality of life

No data from the following reference on this outcome. [19] [22] [38] [39] [16]

Adverse effects

No data from the following reference on this outcome. [19] [22] [38] [39] [16]

Exposure versus cognitive restructuring:
See option on cognitive restructuring, p 22 .

Exposure versus CBT:
See option on CBT versus other psychological treatments, p 10 .

Further information on studies

[39] All four groups significantly improved all panic measures compared with baseline measures (panic free at week 8: 62% with alprazolam plus exposure *v* 47% with alprazolam plus relaxation *v* 43% with placebo plus exposure *v* 47% with placebo plus relaxation; reported as significant, P value not reported). Compared with previous poorer-quality trials, the RCT had three new features: an exposure therapy contrast group, a 6-month treatment-free follow-up, and a low rate of early placebo withdrawals (“non-evaluables”). Exposure consisted of initial education, weekly diary keeping, weekly discussion of diaries with a therapist, and 2 hours of exposure to one or more phobic targets each week.

Comment: None.

OPTION SELF-HELP

- For GRADE evaluation of interventions for Panic disorder, see table, p 62 .
- Exposure to the panic-inducing stimulus is likely to be effective in reducing symptoms.

Benefits and harms

Self-help methods versus no treatment:

We found one systematic review (search date 2002), which identified eight randomised and non-randomised clinical studies comparing self-help versus no treatment in people with panic disorder, agoraphobia, or panic disorder plus agoraphobia. [18] For full details of review methods, see further information about studies.

Symptom severity

Self-help compared with no treatment Self-help may be more effective than no treatment (also including pill placebo and therapy placebo) at improving symptoms (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Anxiety					
[18] Systematic review	People with panic disorder with or without agoraphobia Number of people and RCTs in analysis not specified	**Anxiety** with self-help with no treatment Absolute results not reported	Effect size +0.80 95% CI +0.29 to +1.30 Positive value for effect size means first intervention more effective than comparator; larger value means greater effect The review did not report details of method of randomisation Results should be interpreted with caution (see further information on studies for more details)	◌◌◌	self-help
Depression					
[18] Systematic review	People with panic disorder with or without agoraphobia Number of people and RCTs in analysis not specified	**Depression** with self-help with no treatment Absolute results not reported	Effect size +0.62 95% CI +0.03 to +1.21 Positive value for effect size means first intervention more effective than comparator; larger value means greater effect The review did not report details of method of randomisation Results should be interpreted with caution (see further information on studies for more details)	◌◌◌	self-help
'Clinically significant improvement'					
[18] Systematic review	People with panic disorder with or without agoraphobia Number of people and RCTs in analysis not specified	**Clinically significant improvement (not further defined)** with self-help with no treatment Absolute results not reported	Effect size +0.98 95% CI +0.25 to +1.71 Positive value for effect size means first intervention more effective than comparator; larger value means greater effect The review did not report details of method of randomisation Results should be interpreted with caution (see further information on studies for more details)	◌◌◌	self-help

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[23] RCT **3-armed trial**	36 people with panic disorder In review [19] The third arm assessed the effects of group CBT	**Proportion of people with 'clinical improvement' in frequency of panic attacks (criteria not reported) , end of treatment** 83% with bibliotherapy CBT 25% with waiting list Absolute numbers not reported Treatment was given for 8 weeks followed by 6 months' follow-up	P <0.01 (bibliotherapy CBT *v* waiting list control)	○○○	self-help

Quality of life

No data from the following reference on this outcome. [18] [23]

Adverse effects

No data from the following reference on this outcome. [18] [23]

Self-help methods versus CBT:

We found two systematic reviews (search date 2002, [40] search date 2005) [19] The first review was narrative in character; for full details of methods, inclusion criteria, and conclusions of the first review [40] , see further information about studies. The second review (search date 2005) identified eight controlled studies. [19] It did not perform a meta-analysis and only two RCTs [41] [23] met our inclusion criteria so these are reported below. We also found one subsequent RCT, [27] which is reported below.

Symptom severity

Self-help compared with CBT We don't know whether bibliotherapy self-help or Internet-delivered self-help are more effective than CBT at improving symptoms (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Global symptoms					
[41] RCT	28 people with panic disorder In review [19]	**Proportion of people who were classed as having high end-state functioning , 6 months** 36% with bibliotherapy CBT plus 1 meeting with therapist plus telephone support (3 sessions) 24% with bibliotherapy plus group CBT (4 sessions) Absolute numbers not reported Treatment was given for 7 weeks	P >0.4	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[27] RCT	49 people with panic disorder with or without agoraphobia; diagnosis confirmed by administering a structured clinical interview	**Body sensations questionnaire , 1 year** with Internet-administered (IT) self-help plus minimal therapist contact via email (10 modules) with CBT (10 individual weekly sessions, termed live therapy) Absolute results not reported See further information on studies for more details on treatment regimens	Reported as not significant P value not reported	⟷	Not significant
[27] RCT	49 people with panic disorder with or without agoraphobia; diagnosis confirmed by administering a structured clinical interview	**Agoraphobic cognitions questionnaire , 1 year** with Internet-administered (IT) self-help plus minimal therapist contact via email (10 modules) with CBT (10 individual weekly live sessions) Absolute results not reported See further information on studies for more details on treatment regimens	Reported as not significant P value not reported	⟷	Not significant
Anxiety and depression					
[27] RCT	49 people with panic disorder with or without agoraphobia; diagnosis confirmed by administering a structured clinical interview	**Beck anxiety and depression inventory , 1 year** with Internet-administered (IT) self-help plus minimal therapist contact via email (10 modules) with CBT (10 individual weekly live sessions) Absolute results not reported See further information on studies for more details on treatment regimens	Reported as not significant P value not reported	⟷	Not significant
Agoraphobia					
[27] RCT	49 people with panic disorder with or without agoraphobia; diagnosis confirmed by administering a structured clinical interview	**Mobilitory inventory for agoraphobia (alone or accompanied) , 1 year** with Internet-administered (IT) self-help plus minimal therapist contact via email (10 modules) with CBT (10 individual weekly live sessions) Absolute results not reported See further information on studies for more details on treatment regimens	Reported as not significant P value not reported	⟷	Not significant
'Clinically relevant improvement'					
[23] RCT **3-armed trial**	36 people with panic disorder In review [19] The third arm assessed the effects of group CBT	**Proportion of people with 'clinical improvement' in frequency of panic attacks (criteria not reported) , 6 months** 75% with bibliotherapy CBT 92% with CBT Absolute numbers not reported	P >0.1 (bibliotherapy CBT versus CBT)	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		Treatment was given for 8 weeks followed by 6 months' follow-up			
Freedom from panic disorder					
[27] RCT	49 people with panic disorder with or without agoraphobia; diagnosis confirmed by administering a structured clinical interview	**Proportion of people no longer meeting criteria of panic disorder , 1 year** 92% with Internet-administered (IT) self-help plus minimal therapist contact via email (10 modules) 88% with CBT (10 individual weekly live sessions) Absolute numbers not reported See further information on studies for more details on treatment regimens	Reported as not significant P value not reported	⟷	Not significant

Quality of life

No data from the following reference on this outcome. [19] [41] [27] [23]

Adverse effects

No data from the following reference on this outcome. [19] [41] [27] [23]

Further information on studies

[18] Inclusion criteria of the review were a minimum of four people, and a waiting list, pill placebo, or therapy placebo group: review did not specify that studies had to be randomised. The review calculated effect sizes to determine the additional benefit from active treatment compared with control. The review found no evidence of publication bias in studies that had compared CBT versus waiting list, placebo, behavioural therapy, or combination treatment. However, these results should be interpreted with caution since response rates tend to be greater in pill placebo control groups as opposed to waiting list control groups, and because few studies of CBT used an intention-to-treat analysis.

[40] The review identified 5 RCTs involving a total of 275 people with panic disorder, with or without agoraphobia, of which only three RCTs had at least 6 months' follow-up). It assessed self-management interventions for panic disorders, phobias, and obsessive compulsive disorder. Two of these RCTs (63 people, assessed post-treatment but with no long-term follow-up) used a home-based, internet-delivered self-help programme with minimal therapist input by email, although the other RCT used individual or group CBT with a therapist plus self-study. The review concluded that CBT and self-exposure to panic-provoking stimuli were effective in reducing the frequency of panic attacks, panic-related cognitions, agoraphobic avoidance, anxiety, and depression at follow-up, by allowing subjects to develop skills and coping strategies (data not reported here). The review also suggested that the use of self-help techniques reduced direct contact time with therapists without reducing the efficacy of treatment.

[27] IT self-help modules in this RCT contained components of psychoeducation, socialisation breathing retraining and hyperventilation tests, cognitive restructuring, interoceptive exposure, exposure *in vivo* and relapse prevention and assertiveness training. Live therapy consisted of 10 weekly individual sessions of 45 to 60 minutes with inter-sessional homework

Comment: The authors of the narrative systematic review looking at self-management commented that, because the RCTs used small sample sizes, significant differences between treatment groups would be difficult to find, as would be the precise intervention responsible for improvement. [40] Furthermore, because self-management interventions require a high level of motivation and engagement, they may be less suitable for people with greater levels of distress.

OPTION BREATHING RETRAINING

- For GRADE evaluation of interventions for Panic disorder, see table, p 62 .
- Breathing retraining may be beneficial, but we found insufficient evidence to be sure.

Benefits and harms

Breathing retraining alone versus no treatment:

We found no RCTs of sufficient quality.

Breathing retraining plus CBT versus control:

We found three systematic reviews (search date 2002, [18] 2005, [19] and not reported), [42] which between them identified one RCT on the effects of breathing retraining. [24]

Symptom severity

Breathing retraining plus CBT compared with control Breathing retraining plus CBT may be more effective than a delayed-treatment control at increasing the proportion of people with high end-state function (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Global symptoms					
[24] RCT **3-armed trial**	45 people with DSM-IV-diagnosed panic disorder with or without agoraphobia In review [18] [19] [42] The third arm assessed the effects of CBT alone	**Proportion of people with high end-state function (defined as panic frequency = 0, anxiety on Sheehan Patient-Rated Anxiety Scale <30, and phobic avoidance on the Mobility Inventory Scale <1.5) , end of treatment** 21% with CBT plus breathing retraining (diaphragmatic breathing instruction plus practise homework in sessions 4 and 5) 0% with control (delayed treatment) Absolute numbers not reported	P <0.01 (CBT plus breathing retraining *v* control)	○○○	CBT plus breathing retraining

Quality of life

No data from the following reference on this outcome. [24]

Adverse effects

No data from the following reference on this outcome. [24]

Breathing retraining plus CBT versus CBT alone:

We found three systematic reviews (search date 2002, [18] 2005, [19] and not reported), [42] which identified one RCT on the effects of breathing retraining. [24]

Symptom severity

Breathing retraining plus CBT compared CBT alone We don't know whether breathing retraining plus CBT is more effective than CBT alone at increasing the proportion of people with high end-state function at end of treatment or at 1 year (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Global symptoms					
[24] RCT **3-armed trial**	45 people with DSM-IV-diagnosed panic disorder with or without agoraphobia In review [18] [19] [42] The third arm assessed the effects of control (delayed treatment)	**Proportion of people with high end-state function (defined as panic frequency = 0, anxiety on Sheehan Patient-Rated Anxiety Scale <30, and phobic avoidance on the Mobility Inventory Scale <1.5) , end of treatment** 21% with CBT plus breathing retraining (diaphragmatic breathing instruction plus practise homework in sessions 4 and 5) 38% with CBT alone Absolute numbers not reported	P <0.10 (CBT plus breathing retraining *v* CBT alone)	⟷	Not significant
[24] RCT **3-armed trial**	45 people with DSM-IV-diagnosed panic disorder with or without agoraphobia In review [18] [19] [42] The third arm assessed the effects of control (delayed treatment)	**Proportion of people with high end-state function (defined as panic frequency = 0, anxiety on Sheehan Patient-Rated Anxiety Scale <30, and phobic avoidance on the Mobility Inventory Scale <1.5) , 1 year** 37% with CBT plus breathing retraining (diaphragmatic breathing instruction plus practise homework in sessions 4 and 5) 57% with CBT alone Absolute numbers not reported	P <0.10 (CBT plus breathing retraining *v* CBT alone)	⟷	Not significant

Quality of life

No data from the following reference on this outcome. [24]

Adverse effects

No data from the following reference on this outcome. [24]

Further information on studies

Comment: Breathing retraining is based on the rationale that hypocapnia and respiratory irregularities are underlying factors in the development of panic. The systematic review recommended that these factors should be monitored physiologically throughout treatment and that techniques taught in breathing retraining must take account of respiration rate and tidal volume in the regulation of blood gases (partial pressure of carbon dioxide [pCO_2]). [42]

OPTION BRIEF DYNAMIC PSYCHOTHERAPY

- For GRADE evaluation of interventions for Panic disorder, see table, p 62 .
- Brief dynamic psychotherapy may be beneficial, but we found insufficient evidence to be sure.
- We found no direct information about whether brief dynamic psychotherapy alone is better than no active treatment.

Benefits and harms

Brief dynamic psychotherapy alone versus no treatment:

We found no systematic review or RCTs.

Brief dynamic psychotherapy plus clomipramine versus clomipramine alone:

We found one RCT. [43]

Symptom severity

Brief dynamic psychotherapy plus clomipramine compared with clomipramine alone Brief dynamic psychotherapy plus clomipramine may be more effective at increasing global improvement and at improving panic scores at 18 months, and at decreasing the proportion of people with relapse 9 months after the end of treatment (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Global symptoms					
[43] RCT	40 people	**Global improvement on Clinical Global Impression , 18 months** with brief dynamic psychotherapy plus clomipramine with clomipramine Absolute results not reported People were permitted benzodiazepine treatment during the step-up phase for clomipramine in both groups, and were reviewed at 6, 12, and 18 months by an assessor blinded to treatment	P = 0.001 See further information on studies for discussion of potential effects of adding clomipramine to BDP	○○○	brief dynamic psychotherapy plus clomipramine
Freedom from panic attacks					
[43] RCT	40 people	**Proportion of people who were free from panic attacks , end of treatment** 100% with brief dynamic psychotherapy plus clomipramine 75% with clomipramine Absolute numbers not reported People were permitted benzodiazepine treatment during the step-up phase for clomipramine in both groups, and were reviewed at 6, 12, and 18 months by an assessor blinded to treatment	Significance not assessed See further information on studies for discussion of potential effects of adding clomipramine to BDP		

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[43] RCT	40 people	**Proportion of people who were free from panic attacks , 6 months** 20/20 (100%) with brief dynamic psychotherapy plus clomipramine 20/20 (100%) with clomipramine People were permitted benzodiazepine treatment during the step-up phase for clomipramine in both groups, and were reviewed at 6, 12, and 18 months by an assessor blinded to treatment	Significance not assessed See further information on studies for discussion of potential effects of adding clomipramine to BDP		
Panic					
[43] RCT	40 people	**Improvement in panic subscale of Clinical Global Impression , 18 months** with brief dynamic psychotherapy plus clomipramine with clomipramine Absolute results not reported People were permitted benzodiazepine treatment during the step-up phase for clomipramine in both groups, and were reviewed at 6, 12, and 18 months by an assessor blinded to treatment	P <0.001 See further information on studies for discussion of potential effects of adding clomipramine to BDP	○○○	brief dynamic psychotherapy plus clomipramine
Relapse					
[43] RCT	40 people	**Proportion of people who relapsed , 9 months after the end of treatment** 20% with brief dynamic psychotherapy plus clomipramine 75% with clomipramine Absolute numbers not reported People were permitted benzodiazepine treatment during the step-up phase for clomipramine in both groups, and were reviewed at 6, 12, and 18 months by an assessor blinded to treatment	Reported as significant P value not reported See further information on studies for discussion of potential effects of adding clomipramine to BDP	○○○	brief dynamic psychotherapy plus clomipramine

Quality of life

No data from the following reference on this outcome. [43]

Adverse effects

No data from the following reference on this outcome. [43]

Panic-focused psychodynamic psychotherapy versus applied relaxation:
We found one small RCT. [33]

Symptom severity

Panic-focused psychodynamic psychotherapy versus applied relaxation therapy Panic-focused psychodynamic psychotherapy may be more effective at reducing symptom severity and may be more effective at increasing the proportion of people who respond to treatment (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Global symptoms					
[33] RCT	49 adults with primary diagnosis DSM-IV diagnosis panic disorder	**Mean Panic Disorder Severity Scale score (change from baseline)** From 13.2 to 5.1 with panic-focused psychodynamic psychotherapy From 12.2 to 9.0 with applied relaxation therapy Treatments were given twice weekly over 12 weeks One person in the applied-relaxation group was deemed to require pharmacotherapy and was discharged from the study at week 6	P = 0.002	○○○	PFPP
[33] RCT	49 adults with primary diagnosis DSM-IV diagnosis panic disorder	**Proportion of people classed as a responder (response defined as 40% reduction from baseline in Panic Disorder Severity Scale score)** 19/26 (73%) with panic-focused psychodynamic psychotherapy 9/23 (39%) with applied relaxation therapy Treatments were given twice weekly over 12 weeks One person in the applied-relaxation group was deemed to require pharmacotherapy and was discharged from the study at week 6	P = 0.016	○○○	PFPP

Quality of life

No data from the following reference on this outcome. [33]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Withdrawal					
[33] RCT	49 adults with primary diagnosis DSM-IV diagnosis panic disorder	**Proportion of people withdrawing from RCT** 2/26 (7%) with panic-focused psychodynamic psychotherapy	P = 0.03	○○○	PFPP

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		8/23 (34%) with applied relaxation therapy Treatments were given twice weekly over 12 weeks One person in the applied-relaxation group was deemed to require pharmacotherapy and was discharged from the study at week 6			

Further information on studies

[43] The authors of the RCT suggested that the addition of clomipramine may, by reducing the frequency and intensity of the panic attacks, have reduced the level of psychological distress sufficiently for the people to then be able to work on the issues addressed by BDP. The combined treatment could have maximised the patients' confidence by both ameliorating their panic attacks and providing the opportunity to change their maladaptive interpersonal patterns.

Comment: None.

OPTION COUPLE THERAPY

- For GRADE evaluation of interventions for Panic disorder, see table, p 62 .
- Couple therapy may be beneficial, but we found insufficient evidence to be sure.
- We found no direct information about whether couple therapy is better than no active treatment.

Benefits and harms

Couple therapy versus no treatment:

We found no systematic review or RCTs.

Different forms of couple therapy versus each other:

We found one systematic review (search date 2001), [44] which included three RCTs of sufficient quality. [45] [46] [47]

Symptom severity

Different forms of couple therapy compared with each other Couples communication skills training may be more effective than couples relaxation training at increasing the proportion of people taking unaccompanied excursions and at improving behavioural approach test scores at 8 months. We don't know whether behavioural therapy with husband as co-therapist is more effective than behavioural therapy with a female friend as co-therapist, or whether graded exposure with friends or spouses is more effective than problem solving with friends or spouses at 4 weeks (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Global symptoms					
[45] RCT	30 married women with DSM-III-diagnosed panic disorder with agoraphobia In review [44]	**Mean Behavioural Items score , 6 months** with behavioural therapy at home with a female friend with couple therapy (behavioural therapy at home with husband as co-therapist) Absolute results reported graphically Both treatments significantly improved outcome (P <0.001) compared with baseline measures	Reported as not significant P value not reported	⟷	Not significant
[46] RCT	24 women with DSM-III-diagnosed agoraphobia with panic attacks In review [44]	**Mean Behavioural Approach Test score , 8 months** with couples relaxation training with couples communication skills training Absolute results not reported Therapies were given over 8 weeks Both treatments significantly improved outcome (P <0.001) compared with baseline measures	P <0.02	○○○	couples communication skills training
[46] RCT	24 women with DSM-III-diagnosed agoraphobia with panic attacks In review [44]	**Proportion of people taking unaccompanied excursions , 8 months** with couples relaxation training with couples communication skills training Absolute results not reported Therapies were given over 8 weeks Both treatments significantly improved outcome (P <0.001) compared with baseline measures	P <0.01	○○○	couples communication skills training
Anxiety					
[45] RCT	30 married women with DSM-III-diagnosed panic disorder with agoraphobia In review [44]	**Mean Leeds Anxiety score , 6 months** with behavioural therapy at home with a female friend with couple therapy (behavioural therapy at home with husband as co-therapist) Absolute results reported graphically Both treatments significantly improved outcome (P <0.01) compared with baseline measures	Reported as not significant P value not reported	⟷	Not significant
[47] RCT	28 women with agoraphobia whose main complaint was fear of leaving home and	**Change in physician-assessed ratings of phobic anxiety , 6 months** with programmed practise (graded exposure) at home	Reported as not significant P value not reported	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
	entering public places In review [44]	with problem solving at home Absolute results reported graphically Both therapies were given over 4 weeks and involved willing friends or spouses Both treatments significantly improved outcome compared with baseline measures (P <0.001 for both therapies)			
[47] RCT	28 women with agoraphobia whose main complaint was fear of leaving home and entering public places In review [44]	**Change in participant-assessed ratings of phobic anxiety , 6 months** with programmed practise (graded exposure) at home with problem solving at home Absolute results reported graphically Both therapies were given over 4 weeks and involved willing friends or spouses Both treatments significantly improved outcome compared with baseline measures (P <0.001 with programmed practice and P <0.01 with problem solving)	Reported as not significant P value not reported	⟷	Not significant

Quality of life

No data from the following reference on this outcome. [45] [46] [47]

Adverse effects

No data from the following reference on this outcome. [45] [46] [47]

Further information on studies

Comment: Some cognitive behavioural therapists have encouraged spouse participation on the grounds that the person's adherence with exposure homework assignment will improve. However, the evidence is conflicting. One systematic review (that included no studies that met *Clinical Evidence* inclusion criteria) found that many studies reviewed had small samples, that psychometric data of all measures were not published, and that there was a wide range of variability in parameters used by different studies. [48]

OPTION INSIGHT-ORIENTATED THERAPY

- For GRADE evaluation of interventions for Panic disorder, see table, p 62 .

- We found no direct information from RCTs about whether insight-orientated therapy is better than no active treatment.

Benefits and harms

Insight-orientated therapy:

We found one systematic review (search date 2002), [18] which identified no RCTs of sufficient quality.

Further information on studies

Comment: RCTs are needed. There is currently widespread scepticism about the usefulness of insight-orientated therapy in panic disorder.

OPTION PSYCHOEDUCATION

- For GRADE evaluation of interventions for Panic disorder, see table, p 62 .
- We found no direct information from RCTsa about whether psychoeducation alone is better than no active treatment.

Benefits and harms

Psychoeducation:

We found no systematic review or RCTs of psychoeducation as a sole intervention in the treatment of panic disorder.

Further information on studies

Comment: We found no RCTs evaluating psychoeducation as the sole intervention. Most CBT interventions generally started with educational/informational session(s) providing information on the nature of symptoms experienced during panic attack, and on the roles played by fears, avoidance, and catastrophic misinterpretation in the onset and maintenance of panic symptoms. Such information formed the basis of developing a disorder model of panic disorder, and rationale for the specific intervention to be used in the study.

QUESTION What are the effects of drug treatments for panic disorder?

OPTION SSRIS

- For GRADE evaluation of interventions for Panic disorder, see table, p 62 .
- SSRIs are effective at reducing the symptoms of panic disorder.

Benefits and harms

SSRIs versus placebo:

We found four systematic reviews (search date 2002, [18] 2005, [19] not reported [49] not reported). [50] Two of the reviews [49] [50] systematic reviews were each included in the third review (search date 2002) [18] so are not reported further. The meta-analysis of the third review, which assessed anxiety, is reported below. [18] The fourth systematic review identified 22 placebo-controlled studies, 10 of which were included in the third review. [19] It also performed a meta-analysis assessing global symptom improvement which is reported below. For full details of inclusion criteria

and methods of the reviews, [18] [19] see further information about studies. We also found two additional RCTs. [51] [52]

Symptom severity

SSRIs compared with placebo SSRIs may be more effective at improving symptoms of panic disorder (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Global symptoms					
[51] RCT **5-armed trial**	279 people The fifth arm assessed the effects of oral clomipramine 60 or 90 mg daily	**Proportion of people who responded (defined as no panic attacks and either no episodic increases in anxiety or only slight increases in anxiety precipitated by definite events or activities) , 12 months** with oral citalopram 10 or 15 mg daily with oral citalopram 20 or 30 mg daily with oral citalopram 40 or 60 mg daily with placebo Absolute results reported graphically Flexible dosing regimen, based on tolerance and therapeutic need	Citalopram 10 or 15 mg/day *v* placebo; P = 0.05 Citalopram 20 or 30 mg/day *v* placebo; P = 0.001 Citalopram 40 or 60 mg/day *v* placebo; P = 0.003 Only 28/54 (52%) people completed the trial; analysis was by intention to treat, and people who withdrew from the trial were counted as treatment failures	○○○	citalopram
[52] RCT	182 people who had responded to open label sertraline for 52 weeks	**Proportion of people who had exacerbation of symptoms , 28 weeks** 13% with sertraline 33% with placebo (discontinuation of sertraline) Absolute numbers not reported	P = 0.005 The use of treatment responders was likely to bias results in favour of the drug	○○○	sertraline
[19] Systematic review	People with panic disorder with or without agoraphobia Number of people and RCTs in analysis not specified	**Symptom improvement** with SSRIs for 8 to 12 weeks with placebo Absolute results not reported	NNT 8 95% CI 6 to 11	○○○	SSRIs
[19] Systematic review	People with panic disorder with or without agoraphobia Number of people and RCTs in analysis not specified	**Symptom improvement** with paroxetine for 8 to 12 weeks with placebo Absolute results not reported	NNT 5 95% CI 3 to 7	○○○	paroxetine
[19] Systematic review	People with panic disorder with or without agoraphobia Number of people and RCTs in analysis not specified	**Symptom improvement** with citalopram for 8 to 12 weeks with placebo Absolute results not reported	NNT 5 95% CI 3 to 11	○○○	citalopram
[19]	People with panic disorder with or without agoraphobia	**Symptom improvement** with sertraline for 8 to 12 weeks with placebo	NNT 8 95% CI 5 to 20	○○○	sertraline

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
	Number of people and RCTs in analysis not specified	Absolute results not reported			
Anxiety					
[18] Systematic review	People with panic disorder with or without agoraphobia Number of people and RCTs in analysis not specified	**Anxiety** with SSRIs with placebo Absolute results not reported	Effect size 0.41 Significance and P value not reported Positive value for effect size means first intervention more effective than comparator; larger value means greater effect The review did not report details of method of randomisation		
Depression					
[18] Systematic review	People with panic disorder with or without agoraphobia Number of people and RCTs in analysis not specified	**Depression** with SSRIs with placebo Absolute results not reported	Effect size 0.50 Significance and P value not reported Positive value for effect size means first intervention more effective than comparator; larger value means greater effect The review did not report details of method of randomisation		

Quality of life

No data from the following reference on this outcome. [18] [19] [51] [52]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[51] RCT **5-armed trial**	279 people The fifth arm assessed the effects of oral clomipramine 60 or 90 mg daily	**Adverse effects** with oral citalopram 10 or 15 mg daily with oral citalopram 20 or 30 mg daily with oral citalopram 40 or 60 mg daily with placebo Absolute results not reported The RCT reported that harms associated with citalopram included headache, tremor, dry mouth, and somnolence (see harms of prescription antidepressant drugs in review on depression in adults) Flexible dosing regimen, based on tolerance and therapeutic need	Only 28/54 (52%) people completed the trial; analysis was by intention to treat, and people who withdrew from the trial were counted as treatment failures		

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[52] RCT	182 people who had responded to open label sertraline for 52 weeks	**Adverse effects , 28 weeks** with sertraline with placebo (discontinuation of sertraline) Absolute results not reported The RCT found the highest rate of adverse effects with sertraline in the first 12 weeks of the study, and tolerability seemed to improve with time The most common adverse effects over the 52-week trial period were headache, malaise, insomnia, upper respiratory infection, diarrhoea, nausea, and dizziness			

No data from the following reference on this outcome. [18] [19]

SSRIs versus MAOIs:
See option on MAOIs, p 50 .

SSRIs versus CBT:
See option on CBT versus drug treatment, p 8 .

Further information on studies

[18] The review identified and performed a meta-analysis on results from 78 controlled studies identified by these and by other meta-analyses. The review stated that included studies had to have a control group, but did not specify that they must be randomised.

[19] The review reported only the number needed to treat (NNT) to improve symptoms in one person for all SSRIs and for each drug individually.

Comment:

The second systematic review found that smaller RCTs were associated with larger effect sizes, suggesting the possibility of publication bias. [50]

SSRIs can cause initial increased anxiety, which can exacerbate a tendency to focus on internal sensations, and to avoid situations that trigger these sensations (catastrophisation of somatic sensations). Education about this is likely to improve adherence with medication. The FDA and other regulatory bodies have issued several alerts and revised prescribing information regarding the use of SSRIs, on the increased risk of self-harm and suicide, on increased risk of neonatal persistent pulmonary hypertension in women who had taken SSRIs during pregnancy, on the risk of congenital malformations in women taking paroxetine during early pregnancy, and on the potential for SSRIs to cause hyponatraemia. [53] [54] [55] [56] See harms of prescription antidepressant drugs in review on depression in adults (drug and other physical treatments)

Tricyclic antidepressants versus SSRIs:
See comment on tricyclic antidepressants, p 44 .

OPTION TRICYCLIC ANTIDEPRESSANTS

- For GRADE evaluation of interventions for Panic disorder, see table, p 62 .
- Tricyclic antidepressants are effective at reducing the symptoms of panic disorder.

Benefits and harms

Tricyclic antidepressants versus placebo:

We found three systematic reviews, [18] [19] [49] and two additional RCTs. [57] [58] The first systematic review [49] was included in the second review (search date 2002) [18] so is not reported further. The meta-analysis of the second review, assessing anxiety and depression, is reported below. [18] The third systematic review (search date 2005) [19] identified 21 placebo-controlled studies, 10 of which were included in the second review. [18] It performed a meta-analysis assessing global symptom improvement, which is reported below.

Symptom severity

Tricyclic antidepressants compared with placebo Tricyclic antidepressants may be more effective at improving symptoms of panic disorder (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Global symptoms					
[19] Systematic review	People with panic disorder with or without agoraphobia Number of people and RCTs in analysis not specified	**Symptom improvement** with tricyclic antidepressants for 6 to 12 weeks with placebo Absolute results not reported	NNT 6 95% CI 5 to 8		
[19] Systematic review	People with panic disorder with or without agoraphobia Number of people and RCTs in analysis not specified	**Symptom improvement** with imipramine for 6 to 12 weeks with placebo Absolute results not reported	NNT 6 95% CI 4 to 8		
[19] Systematic review	People with panic disorder with or without agoraphobia Number of people and RCTs in analysis not specified	**Symptom improvement** with clomipramine for 6 to 12 weeks with placebo Absolute results not reported	NNT 7 95% CI 4 to 17		
Anxiety					
[18] Systematic review	People with panic disorder with or without agoraphobia Number of people and RCTs in analysis not specified	**Anxiety** with tricyclic antidepressants with placebo Absolute results not reported	Effect size 0.41 Significance and P value not reported Positive value for effect size means first intervention more effective than comparator; larger value means greater effect The review did not report details of method of randomisation		
Depression					
[18] Systematic review	People with panic disorder with or without agoraphobia Number of people and RCTs in analysis not specified	**Depression** with tricyclic antidepressants with placebo	Effect size 0.34 Significance and P value not reported Positive value for effect size means first intervention more ef-		

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		Absolute results not reported	fective than comparator; larger value means greater effect The review did not report details of method of randomisation		
Frequency of panic attack					
[57] RCT **3-armed trial**	181 people with panic disorder with or without agoraphobia The third arm assessed the effects of oral alprazolam (maximum dose 10 mg)	**Frequency of panic attack , 8 months** with oral imipramine (maximum dose 225 mg) with placebo Absolute results reported graphically Flexible dosing was used according to tolerance and therapeutic need	Significance not assessed Results favoured imipramine		
Relapse					
[58] RCT	56 adults with panic disorder and agoraphobia in stable remission after 24 weeks' treatment with oral imipramine	**Proportion of people relapsing , 12 months** 1/29 (3%) with oral imipramine 2.25 mg/kg daily 10/27 (37%) with placebo	RR 0.09 95% CI 0.01 to 0.68 NNT 5 95% CI 3 to 14	●●●	imipramine

Quality of life

No data from the following reference on this outcome. [18] [19] [57] [58]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[57] RCT **3-armed trial**	181 people with panic disorder with or without agoraphobia The third arm assessed the effects of oral alprazolam (maximum dose 10 mg)	**Adverse effects** with oral imipramine (maximum dose 225 mg) with placebo Adverse effects associated with imipramine treatment included blurred vision, tachycardia, palpitations, blood pressure changes, insomnia, nervousness, malaise, dizziness, headache, nausea, vomiting, and reduced appetite (see harms of prescription antidepressant drugs in review on depression on adults) Flexible dosing was used according to tolerance and therapeutic need			

No data from the following reference on this outcome. [18] [19] [58]

Tricyclic antidepressants versus CBT:

See option on CBT versus drug treatment, p 8 .

Further information on studies

[18] The review identified and performed a meta-analysis on results from 78 controlled studies identified by this and by other meta-analyses. The review stated that included studies had to have a control group but did not specify that they had to be randomised.

[19] The review performed a meta-analysis and calculated the number needed to treat (NNT) to improve symptoms in one person for each type of drug intervention compared with placebo.

Comment:

Short-term effects:

We found one systematic review (search date 1999, 43 studies including 34 RCTs, 2367 people, withdrawal rate 24%, analysis based on completers) that compared the short-term efficacy of SSRIs (fluoxetine, fluvoxamine, paroxetine, citalopram, and sertraline) versus tricyclic antidepressants (imipramine, desipramine, nortriptyline, and clomipramine) and analysed effect size within treatment group rather than within studies. [59] It found no significant difference between treatments in the proportion of people free of panic attacks at 6 to 10 weeks (60% with tricyclic antidepressants *v* 55% with SSRIs; P value not reported). It found that tricyclic antidepressants significantly increased withdrawal rates (31% with tricyclic antidepressants *v* 18% with SSRIs; P <0.001). These results should be interpreted with caution because nine of the RCTs were open label and there was no indication of the length of follow-up for any of the RCTs.

OPTION BENZODIAZEPINES

- For GRADE evaluation of interventions for Panic disorder, see table, p 62 .
- Benzodiazepines can be effective in reducing symptoms in panic disorder, but their adverse-effect profile makes them unsuitable for long-term treatment.
- Benzodiazepines are associated with a wide range of well-recognised adverse effects, both during and after treatment.

Benefits and harms

Benzodiazepines versus placebo:

We found five systematic reviews, [18] [19] [49] [60] [61] The first systematic review [49] was included in the second review (search date 2002) [18] so is not reported further. The second review performed a meta-analysis anxiety and depression, which is reported below. The third systematic review (search date 2005) [19] identified 27 placebo-controlled studies, 17 of which were included in the second review. [18] It performed a meta-analysis assessing global symptoms, which is reported below. For full details of inclusion criteria and methods of these two reviews, [18] [19] see further information about studies. The fourth systematic review was excluded as the RCTs included did not meet *Clinical Evidence* inclusion criteria. [60] The fifth review (search date 2006, 16 RCTs published from 1986–1999) assessed alprazolam versus placebo and performed a meta-analysis assessing global symptom improvement, which is reported below. [61]

Symptom severity

Benzodiazepines compared with placebo Benzodiazepines may be more effective at improving symptoms of panic disorder (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Global symptoms					
[19] Systematic review	People with panic disorder with or without agoraphobia Number of people and RCTs in analysis not specified	**Symptom improvement** with alprazolam for 5 to 8 weeks with placebo Absolute results not reported	NNT 5 95% CI 4 to 7		
[19] Systematic review	People with panic disorder with or without agoraphobia Number of people and RCTs in analysis not specified	**Symptom improvement** with clonazepam for 5 to 8 weeks with placebo Absolute results not reported	NNT 5 95% CI 4 to 7		
Anxiety					
[18] Systematic review	People with panic disorder with or without agoraphobia Number of people and RCTs in analysis not specified	**Anxiety** with benzodiazepines with placebo Absolute results not reported	Effect size 0.40 Significance and P value not reported Positive value for effect size means first intervention more effective than comparator; larger value means greater effect The review did not report details of method of randomisation		
Depression					
[18] Systematic review	People with panic disorder with or without agoraphobia Number of people and RCTs in analysis not specified	**Depression** with benzodiazepines with placebo Absolute results not reported	Effect size 0.28 Significance and P value not reported Positive value for effect size means first intervention more effective than comparator; larger value means greater effect The review did not report details of method of randomisation		
Freedom from panic attacks					
[61] Systematic review	1669 people 8 RCTs in this analysis Details of individual RCT sizes were not reported	**Proportion of people free from panic attacks** 64% with alprazolam 41% with placebo Absolute numbers not reported Duration of treatment and regimen used in each RCT was not reported	RR 0.61 95% CI 0.52 to 0.71	●○○	benzodiazepine

Quality of life

No data from the following reference on this outcome. [18] [61] [19]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[57]		**Adverse effects** with benzodiazepines with placebo Adverse effects associated with alprazolam include sedation, insomnia, memory lapses, nervousness, irritability, dry mouth, tremor, impaired coordination, constipation, urinary retention, altered libido, and altered appetite (see harms of benzodiazepines in review on generalised anxiety disorder)			
[62] Non-systematic review	People with a history of substance abuse or dependence and anxiety disorder	**Adverse effects** with benzodiazepines with placebo The review reported that mortality in long-term benzodiazepine users was no higher than that of matched controls The most pronounced adverse effects followed sudden withdrawal, and included tinnitus, paraesthesia, vision disturbance, depersonalisation, seizures, withdrawal psychosis, and persistent discontinuation syndrome			
Withdrawal					
[61] Systematic review	2284 people 14 RCTs in this analysis Details of individual RCT sizes were not reported	**Proportion of people withdrawing (reasons for withdrawal not further defined)** 15% with alprazolam 44% with placebo Absolute numbers not reported Duration of treatment and regimen used in each RCT was not reported	RR 0.22 95% CI 0.18 to 0.27	●●○	benzodiazepine

No data from the following reference on this outcome. [19]

Further information on studies

[18] The review identified and performed a meta-analysis on results from 78 controlled studies identified by this and by other meta-analyses. Mean effect sizes for benzodiazepines were similar to those of SSRIs and of tricyclic antidepressants for reduction of anxiety and depression scores. The review stated that included studies had to have a control group but did not specify that they had to be randomised.

[19] The review performed a meta-analysis and calculated the number needed to treat (NNT) to improve symptoms in one person for each type of drug intervention compared with placebo.

Comment: Many RCTs of psychological and pharmacological treatments (even those not involving benzodiazepines) allowed people to receive small amounts of anxiolytic drugs during the study, because

benzodiazepine use and abuse is quite prevalent in people who suffer from panic disorder. We found one systematic review with meta-analysis of placebo-controlled RCTs of antidepressants and benzodiazepines for the treatment of panic disorders (search date 1990, 1276 people, 13 antidepressant trials, mean duration 16 weeks; 6 benzodiazepine trials, mean duration 7 weeks) that found that antidepressants and benzodiazepines were likely to be equally effective in the short-term treatment of panic disorder. [60] However, longer-term follow-up was not performed in any of the RCTs of benzodiazepine treatment.

OPTION BUSPIRONE

- For GRADE evaluation of interventions for Panic disorder, see table, p 62 .
- We don't know whether buspirone is effective in the treatment of panic disorder.
- We found no direct information from RCTs about whether buspirone is better than no active treatment.

Benefits and harms

Oral buspirone alone versus placebo:

We found no RCTs.

Oral buspirone plus CBT versus placebo plus CBT:

We found two systematic reviews [18] [19] which identified one RCT, [63] and we found one additional RCT. [64] The RCTs gave no information on adverse effects. For information on adverse effects of buspirone, see harms of buspirone in review on generalised anxiety disorder.

Symptom severity

Oral buspirone plus CBT versus placebo plus CBT We don't know whether oral buspirone plus CBT is more effective at improving symptoms (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Panic and agoraphobia					
[63] RCT	41 people with panic disorder and agoraphobia In review [18] [19]	**Proportion of people with a reduction of at least 50% in agoraphobic symptoms , 68 weeks** 44% with oral buspirone 30 mg daily plus CBT 68% with placebo plus CBT Absolute numbers not reported Treatments were given over 16 weeks	Reported as not significant P value not reported	⟷	Not significant
[64] RCT	48 people	**Improvement in self-rated panic and agoraphobia scores (using a 90-point symptom scale where each symptom was graded from 0 = not present to 4 = severe) , 1 year** with oral buspirone (maximum 60 mg/day) plus CBT with placebo plus CBT Absolute results not reported Treatments were given over 16 weeks Flexible dosing regimen of buspirone with maximum dose adjustment according to tolerance and therapeutic need	P = 0.03	○○○	oral buspirone plus CBT

Quality of life

No data from the following reference on this outcome. [63] [64]

Adverse effects

No data from the following reference on this outcome. [63] [64]

Further information on studies

Comment: None.

OPTION MAOIS

- For GRADE evaluation of interventions for Panic disorder, see table, p 62 .
- We don't know whether MAOIs are effective.

Benefits and harms

MAOIs versus control or placebo:

We found one systematic review (search date 2005), [19] which identified no controlled studies of MAOIs meeting our inclusion criteria for this comparison.

MAOIs versus SSRIs:

We found one systematic review (search date 2005), [19] which identified four controlled studies of MAOIs, one of which met our inclusion criteria. [65]

Symptom severity

MAOIs compared with SSRIs We don't know whether moclobemide is more effective than fluoxetine at reducing the proportion of people who are panic free at 1 year (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Freedom from panic attacks					
[65] RCT	366 people with panic disorder	**Proportion of people who were panic free , 1 year** 60% with moclobemide 300 to 600 mg daily 65% with fluoxetine 10 to 30 mg daily Absolute numbers not reported Treatments were given for 8 weeks	Reported as not significant P value not reported	⟷	Not significant

Quality of life

No data from the following reference on this outcome. [65]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[65] RCT	366 people	**Adverse effects** with moclobemide 300 to 600 mg daily with fluoxetine 10 to 30 mg daily The RCT gave no information on adverse effects for the comparison of moclobemide versus fluoxetine, but reported data on adverse effects of moclobemide from a safety database of 624 people (see further information on studies for details)			

Further information on studies

[65] The safety database found that, compared with placebo, moclobemide was associated with higher rates of insomnia (24% with moclobemide *v* 13% with placebo), and dizziness (11% with moclobemide *v* 7% with placebo; P values not reported). There was no significant difference in blood pressure changes with moclobemide at doses less than 300 mg daily, 300 mg to 599 mg daily, or 600 mg or more daily, compared with placebo.

Comment: None.

QUESTION What are the effects of combined drug and psychological treatments for panic disorder?

OPTION CBT PLUS DRUG TREATMENTS VERSUS CBT ALONE

- For GRADE evaluation of interventions for Panic disorder, see table, p 62 .
- Combined treatment with CBT plus antidepressants has been shown to be more effective than CBT alone in reducing symptoms in the short term.

Benefits and harms

CBT plus antidepressants versus CBT alone:

We found two systematic reviews (search date 2002, [18] search date 2005), [18] which pooled data and performed slightly different analysis so both are reported here. [66] For full details of methods and inclusion criteria of reviews, see further information about studies.

Symptom severity

CBT plus antidepressants compared with CBT alone CBT plus antidepressants may be more effective at improving the proportion of people in remission and at decreasing global severity of symptoms in the acute phase at 2 to 4 months, but not at improving the proportion of people with response at 2 to 4 months. We don't know whether CBT

plus antidepressants is more effective at improving response/remission with continued treatment after the acute phase, or at improving response/remission 6 to 24 months after treatment discontinuation (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Global symptoms					
[66] Systematic review	363 people 3 RCTs in this analysis	**Global severity of symptoms in the acute phase , 2 to 4 months** with CBT plus antidepressant with CBT or CBT plus placebo Absolute results not reported Antidepressants included tricyclic antidepressants, SSRIs, MAOIs, serotonin-noradrenaline reuptake inhibitors, and others (e.g., bupropion, trazodone)	SMD –0.31 95% CI –0.54 to –0.08 Control group was a combined analysis of CBT alone and CBT plus placebo (see further information on studies for comments on this and generalisability)	○○○	CBT plus antidepressant
[66] Systematic review	709 people 9 RCTs in this analysis	**Proportion of people with response to treatment in the acute phase , 2 to 4 months** 187/310 (60%) with CBT plus antidepressant 211/399 (53%) with CBT or CBT plus placebo Antidepressants included tricyclic antidepressants, SSRIs, MAOIs, serotonin-noradrenaline reuptake inhibitors, and others (e.g., bupropion, trazodone)	RR 1.13 95% CI 0.96 to 1.33 Control group was a combined analysis of CBT alone and CBT plus placebo (see further information on studies for comments on this and generalisability)	⟷	Not significant
[66] Systematic review	205 people Data from 1 RCT	**Proportion of people with response/remission after acute phase , > 4 months** 37/65 (60%) with CBT plus antidepressant 64/140 (46%) with CBT or CBT plus placebo Antidepressants included tricyclic antidepressants, SSRIs, MAOIs, serotonin-noradrenaline reuptake inhibitors, and others (e.g., bupropion, trazodone)	RR 1.23 95% CI 0.93 to 1.63 Control group was a combined analysis of CBT alone and CBT plus placebo (see further information on studies for comments on this and generalisability)	⟷	Not significant
[66] Systematic review	339 people 3 RCTs in this analysis	**Proportion of people with response/remission after acute phase , 6 to 24 months after treatment discontinuation** 41/111 (37%) with CBT plus antidepressant 90/228 (40%) with CBT or CBT plus placebo Antidepressants included tricyclic antidepressants, SSRIs, MAOIs, serotonin-noradrenaline reuptake inhibitors, and others (e.g., bupropion, trazodone)	RR 0.91 95% CI 0.69 to 1.21 Control group was a combined analysis of CBT alone and CBT plus placebo (see further information on studies for comments on this and generalisability)	⟷	Not significant
Anxiety					
[18] Systematic review	People with panic disorder with or without agoraphobia Number of people and RCTs in analysis not specified	**Anxiety , median follow-up of 16.8 months** with CBT plus antidepressant with CBT	Effect size +0.23 95% CI +0.09 to +0.37 Positive value for effect size means first intervention more effective than comparator; larger value means greater effect	○○○	CBT plus antidepressant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		Absolute results not reported	The review did not report details of method of randomisation Results should be interpreted with caution (see further information on studies for more details)		
Depression					
[18] Systematic review	People with panic disorder with or without agoraphobia Number of people and RCTs in analysis not specified	**Depression , median follow-up of 16.8 months** with CBT plus antidepressant with CBT Absolute results not reported	Effect size +0.29 95% CI +0.09 to +0.49 Positive value for effect size means first intervention more effective than comparator; larger value means greater effect The review did not report details of method of randomisation Results should be interpreted with caution (see further information on studies for more details)	○○○	CBT plus antidepressant
'Clinically significant improvement'					
[18] Systematic review	People with panic disorder with or without agoraphobia Number of people and RCTs in analysis not specified	**Clinically significant improvement (not further defined) , median follow-up of 16.8 months** with CBT plus antidepressant with CBT Absolute results not reported	Effect size +0.40 95% CI +0.23 to +0.56 Positive value for effect size means first intervention more effective than comparator; larger value means greater effect The review did not report details of method of randomisation Results should be interpreted with caution (see further information on studies for more details)	○○○	CBT plus antidepressant
Remission					
[66] Systematic review	625 people 7 RCTs in this analysis	**Proportion of people in remission , 2 to 4 months** 160/268 (60%) with CBT plus antidepressant 178/357 (50%) with CBT or CBT plus placebo Antidepressants included tricyclic antidepressants, SSRIs, MAOIs, serotonin-noradrenaline reuptake inhibitors, and others (e.g., bupropion, trazodone)	RR 1.23 95% CI 1.02 to 1.47 Control group was a combined analysis of CBT alone and CBT plus placebo (see further information on studies for comments on this and generalisability)	●○○	CBT plus antidepressant

Quality of life

CBT plus antidepressants compared with CBT alone We don't know whether CBT plus drug treatment (mainly antidepressants but also included other drugs) is more effective (analysis also included behavioural therapy) at improving quality of life (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Quality of life					
[18] Systematic review	People with panic disorder with or without agoraphobia	**Quality of life , median follow-up of 16.8 months** with CBT plus antidepressant with CBT	Effect size +0.25 95% CI –0.18 to +0.68 Positive value for effect size means first intervention more ef-	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
	Number of people and RCTs in analysis not specified	Absolute results not reported	fective than comparator; larger value means greater effect The review did not report details of method of randomisation Results should be interpreted with caution (see further information on studies for more details)		

Adverse effects

CBT plus antidepressants compared with CBT alone CBT plus antidepressants may increase the proportion of people discontinuing treatment due to adverse effects compared with CBT alone (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Withdrawal					
[66] Systematic review	604 people 6 RCTs in this analysis	**Proportion of people who withdrew because of adverse effects , 2 to 4 months** 25/258 (10%) with CBT plus antidepressant 2/346 (1%) with CBT or CBT plus placebo Antidepressants included tricyclic antidepressants, SSRIs, MAOIs, serotonin-noradrenaline reuptake inhibitors, and others (e.g., bupropion, trazodone)	RR 5.00 95% CI 1.96 to 12.72 Control group was a combined analysis of CBT alone and CBT plus placebo (see further information on studies for comments on this and generalisability)	●●●	CBT alone

No data from the following reference on this outcome. [18]

CBT plus buspirone versus CBT alone:

See option on buspirone, p 49 .

Further information on studies

[18] The review (search date 2002) identified 20 studies comparing psychotherapy (CBT or behavioural therapy) with combined psychotherapy plus pharmacotherapy (mainly antidepressants). The drugs investigated were mainly SSRIs and tricyclic antidepressants. Effect sizes were calculated to determine the additional benefit from active treatment compared with control. The review stated that included studies had to have a control group but did not specify that they had to be randomised. The review found some evidence of publication bias in studies that had compared CBT with drug treatment. Adjustment for this led to an increased calculated effect size for CBT compared with drug treatment, but the authors did not report the change in effect size for combined treatment. These results should therefore be interpreted with caution, as pill placebo response rates tend to be greater than those for waiting list control groups, and because few studies of CBT used an intention-to-treat analysis.

[66] The review (search date 2005) compared psychotherapy plus antidepressant versus psychotherapy alone or psychotherapy plus placebo in people with panic disorder with or without agoraphobia. It reported both short- and long-term outcomes and included only RCTs. The review included any type of psychotherapy (including 9 RCTs of CBT consisting of both behavioural and cognitive therapy elements; 12 RCTs of behavioural therapy [including exposure and/or breathing retraining and/or relaxation]; and 2 RCTs of "psychodynamic and others"). It presented pooled results for all psychotherapies, but also presented a subgroup analysis for RCTs of CBT alone which we have reported here. The review included RCTs in which benzodiazepines were used irregularly.

The combination of CBT alone and CBT plus placebo as the control comparison was a post hoc analysis, and the review also reported CBT plus antidepressants versus CBT alone, and CBT plus antidepressants versus CBT plus placebo, separately. Overall, the results were broadly similar in all the analyses, but the significance of some results were sensitive to the method of analysis used. The review noted that the generalisability of the findings beyond specialist psychiatric settings was not straightforward, as only one RCT was undertaken in a primary care setting. It also noted the comparability of treatment arms after the acute phase or continuation phase may have been compromised, as people were free to have other treatments before the final follow-up assessment, and 30% to 77% of people did so.

Comment: None.

OPTION CBT PLUS DRUG TREATMENTS VERSUS DRUGS ALONE

- For GRADE evaluation of interventions for Panic disorder, see table, p 62 .
- Combined treatment with CBT plus antidepressants has been shown to be more effective than antidepressants alone in reducing symptoms in the short term.

Benefits and harms

CBT plus antidepressants versus antidepressants alone:

We found one systematic review (search date 2005) [66] and one subsequent RCT [67] with two subsequent analyses. [68] [69] For full details of inclusion criteria and methods of review, see further information on studies.

Symptom severity

CBT plus antidepressants compared with antidepressants alone CBT plus antidepressants may be more effective at increasing the proportion of people who respond and at decreasing the global severity of symptoms in the acute phase at 2 to 4 months, but not at increasing remission at 2 to 4 months. CBT plus antidepressants may be more effective at improving response/remission with continued treatment after the acute phase, or when assessed at 6 to 24 months after discontinuation of treatment, although results at 6 to 24 months are of borderline significance (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Global symptoms					
[66] Systematic review	336 people 5 RCTs in this analysis	**Proportion of people who responded in the acute phase , 2 to 4 months** 94/159 (59%) with CBT plus antidepressant 74/177 (42%) with antidepressants alone Antidepressants included tricyclic antidepressants, SSRIs, MAOIs, serotonin-noradrenaline reuptake inhibitors, and others (e.g., bupropion, trazodone)	RR 1.46 95% CI 1.05 to 2.02 The review noted that the results may not be generalisable beyond specialist psychiatric settings (see further information on studies for more details)	●○○	CBT plus antidepressant
[66] Systematic review	206 people 2 RCTs in this analysis	**Global severity of symptoms , 2 to 4 months** with CBT plus antidepressant with antidepressants alone Absolute results not reported Antidepressants included tricyclic antidepressants, SSRIs, MAOIs, serotonin-noradrenaline reuptake inhibitors, and others (e.g., bupropion, trazodone)	SMD –0.30 95% CI –0.57 to –0.02 The review noted that the results may not be generalisable beyond specialist psychiatric settings (see further information on studies for more details)	○○○	CBT plus antidepressant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[66] Systematic review	148 people Data from 1 RCT	**Proportion of people responding or in remission after acute phase , >4 months** 37/65 (57%) with CBT plus antidepressant 31/83 (37%) with antidepressants alone Antidepressants included tricyclic antidepressants, SSRIs, MAOIs, serotonin-noradrenaline reuptake inhibitors, and others (e.g., bupropion, trazodone)	RR 1.52 95% CI 1.07 to 2.16 The review noted that the results may not be generalisable beyond specialist psychiatric settings (see further information on studies for more details)	●○○	CBT plus antidepressant
[66] Systematic review	240 people 3 RCTs in this analysis	**Proportion of people responding or in remission , 6 to 24 months after treatment discontinuation** 41/111 (37%) with CBT plus antidepressant 32/129 (25%) with antidepressants alone Antidepressants included tricyclic antidepressants, SSRIs, MAOIs, serotonin-noradrenaline reuptake inhibitors, and others (e.g., bupropion, trazodone)	RR 1.46 95% CI 1.00 to 2.11 P = 0.05 Result is of borderline significance The review noted that the results may not be generalisable beyond specialist psychiatric settings (see further information on studies for more details)	⟷	Not significant
Anxiety					
[67] RCT	232 people in primary-care, meeting DSM-IV criteria for panic disorder, with or without co-morbid mental and physical disorders See further information for details of subgroup analysis based on burden of chronic medical illness at baseline [69]	**Proportion of people responding (achieving a score of <20 on the Anxiety Sensitivity Index scale) , 12 months** 63% with CBT plus pharmacotherapy 38% with usual care Absolute numbers not reported CBT plus antidepressant consisted of up to six sessions of CBT (modified for primary-care setting) with up to six follow-up telephone contacts plus pharmacotherapy (antidepressants as first line, or adjunctive medications [e.g., benzodiazepines]) The usual-care group received pharmacotherapy that was not significantly different from that given to the intervention group	P <0.001	○○○	CBT plus pharmacotherapy
[68] RCT	232 people in primary-care, meeting DSM-IV criteria for panic disorder, with or without co-morbid mental and physical disorders Further report of reference [67]	**Number of anxiety-free days , over a 12 month period** with CBT plus pharmacotherapy with usual care Absolute results not reported CBT plus antidepressant consisted of up to six sessions of CBT (modified for primary-care setting) with up to six follow-up telephone contacts plus pharmacotherapy (antidepressants as first line, or adjunctive medications [e.g., benzodiazepines]) The usual-care group received pharmacotherapy that was not	Difference between groups: +60.4 anxiety-free days 95% CI 42.9 anxiety-free days to 77.9 anxiety-free days See further information for details of subgroup analysis based on burden of chronic medical illness at baseline [69]	○○○	CBT plus pharmacotherapy

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		significantly different from that given to the intervention group			
Remission					
[66] Systematic review	252 people 3 RCTs in this analysis	**Proportion of people in remission , 2 to 4 months** 75/117 (69%) with CBT plus antidepressant 62/135 (46%) with antidepressants alone Antidepressants included tricyclic antidepressants, SSRIs, MAOIs, serotonin-noradrenaline reuptake inhibitors, and others (e.g., bupropion, trazodone)	RR 1.40 95% CI 0.92 to 2.14 The review noted that the results may not be generalisable beyond specialist psychiatric settings (see further information on studies for more details)	⟷	Not significant
[67] RCT	232 people in primary-care, meeting DSM-IV criteria for panic disorder, with or without co-morbid mental and physical disorders	**Proportion of people achieving remission of panic disorder (no panic attacks in the past month, minimal anticipatory anxiety about panic and agoraphobia subscale score of 10 or lower) , 12 months** 29% with CBT plus pharmacotherapy 16% with usual care Absolute numbers not reported CBT plus antidepressant consisted of up to six sessions of CBT (modified for primary-care setting) with up to six follow-up telephone contacts plus pharmacotherapy (antidepressants as first line, or adjunctive medications [e.g., benzodiazepines]) The usual-care group received pharmacotherapy that was not significantly different from that given to the intervention group	P <0.001 See further information for details of subgroup analysis based on burden of chronic medical illness at baseline [69]	○○○	CBT plus pharmacotherapy

Quality of life

No data from the following reference on this outcome. [66] [67] [68]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Withdrawal					
[66] Systematic review	262 people 3 RCTs in this analysis	**Proportion of people who withdrew because of adverse effects , 2 to 4 months** 11/123 (9%) with CBT plus antidepressant 17/139 (12%) with antidepressants alone	RR 0.81 95% CI 0.25 to 2.68 The review noted that the results may not be generalisable beyond specialist psychiatric settings (see further information on studies for more details)	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		Antidepressants included tricyclic antidepressants, SSRIs, MAOIs, serotonin-noradrenaline reuptake inhibitors, and others (e.g., bupropion, trazodone)			

No data from the following reference on this outcome. [67]

Further information on studies

[66] The systematic review (search date 2005) compared psychotherapy plus antidepressant treatment versus antidepressant treatment alone in people with panic disorder with or without agoraphobia, and reported short- and long-term outcomes. The review only included RCTs. [66] It included any type of psychotherapy (including 9 RCTs of CBT consisting of both behavioural and cognitive therapy elements, 12 RCTs of behavioural therapy [including exposure and/or breathing retraining and/or relaxation], and two RCTs of "psychodynamic and others"). It presented pooled results for all psychotherapies, but also presented a subgroup analysis for RCTs of CBT alone which we have reported here. The review included RCTs in which benzodiazepines were used irregularly. The review noted that the generalisability of the findings beyond specialist psychiatric settings was not, straightforward as only one RCT was done in a primary-care setting. It also noted the comparability of treatment arms after the acute phase or continuation phase may have been compromised, as people were free to have other treatments before the final follow-up assessment, and 30% to 77% of people did so.

[69] The subgroup analysis compared outcomes in people above (125 people) versus below (107 people) the median for burden of chronic medical illness at baseline, as assessed by self-reported chronic illness and prescribing data. Those above the median for medical illness were more likely to be older, female, and poorer, and had significantly more psychiatric morbidity at baseline. Both morbidity groups responded to combined CBT plus psychotherapy to a similar extent, but the higher baseline scores in the higher morbidity group meant that this group had higher levels of residual symptoms after treatment. The authors concluded that combined CBT plus pharmacotherapy for panic disorder worked equally well regardless of medical illness co-morbidity, but suggested that more intensive treatment may be required for people with co-morbid medical illnesses.

Comment: None.

GLOSSARY

Cognitive behavioural therapy (CBT) Brief structured treatment using relaxation and exposure procedures, and aimed at changing dysfunctional beliefs and negative automatic thoughts (typically 20 sessions over 12–16 weeks).

Cognitive restructuring An intervention that involves asking questions to help people challenge the stereotyped and repetitive thoughts and images that enhance fear.

Couple therapy An intervention that involves using significant relationships to help change previous persistent and inflexible patterns of behaviour.

Hamilton Depression Rating Scale a measure of depressive symptoms using 17 items, with total scores from 0 to 54 (higher scores indicate increased severity of depression).

Psychoeducation An intervention aimed at educating the person with psychiatric disorder in subject areas that serve the goals of treatment and rehabilitation.

Applied relaxation A technique involving training in relaxation techniques and self-monitoring of symptoms without challenging beliefs.

Beck Depression Inventory Standardised scale to assess depression. This instrument consists of 21 items to assess the intensity of depression. Each item is a list of 4 statements (rated 0, 1, 2, or 3), arranged in increasing severity, about a particular symptom of depression. The range of scores possible are 0 = least severe depression to 63 = most severe depression. It is recommended for people aged 13 to 80 years. Scores of more than 12 or 13 indicate the presence of depression.

Behavioural therapy is a type of psychotherapy which is aimed at modifying the behaviour causing distress or impairment, by focusing on the environment and context in which the behaviour occurs. Unlike other psychotherapies,

behavioural therapy doesn't endorse mind–body split or the impact of past developmental issues, and treats the person as a unit.

Client-centred therapy A system of psychotherapy based on the view that the client has the internal resources to improve and is in the best position to resolve his or her own personality dysfunction. It has roots in psychoanalysis and sees clients as taking a more active role in their treatment.

Clinical Global Impression Scale A one-item, observer-rated scale for measuring the severity of a condition. It has been investigated for validity and reliability. The scale is scored from 0 (not ill at all) to 7 (severely ill).

Exposure A type of behavioural therapy involving deliberate exposure to previously avoided situation or feared stimuli (including thoughts). It can be done by either asking the person to imagine being in the previously avoided situation, especially when direct exposure is impractical or difficult (such as when a person has a fear of flying) — termed in vitro, interoceptive, or imaginal exposure. Alternatively, exposure can be in vivo or exteroceptive, in which exposure is to real life situations or stimuli.

Hamilton Anxiety Rating Scale A 14-item observer-rated scale for measuring the severity of anxiety. It has been investigated for validity and reliability. Each item is rated on a 5-point scale from 0 (no symptoms) to 4 (severe or grossly disabling symptoms). Total score ranges from 0 to 56, with 14 or higher indicating clinically significant anxiety.

Low-quality evidence Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low-quality evidence Any estimate of effect is very uncertain.

SUBSTANTIVE CHANGES

Applied relaxation One small RCT (49 people) added comparing applied relaxation therapy versus panic-focused psychodynamic psychotherapy. [33] It found that panic-focused psychodynamic psychotherapy increased response compared with applied relaxation. Categorisation of 'applied relaxation' unchanged (Likely to be beneficial).

Benzodiazepines One systematic review (search date 2006) added which compared alprazolam versus placebo, and found that alprazolam significantly increased the proportion of people free from panic attacks compared with placebo. [61] Categorisation of benzodiazepines unchanged (Trade-off between benefits and harms).

Brief dynamic psychotherapy One small RCT (49 people) added comparing panic-focused psychodynamic psychotherapy versus applied relaxation therapy. [33] It found that panic-focused psychodynamic psychotherapy increased response compared with applied relaxation. Categorisation of 'Brief dynamic psychotherapy' unchanged (Unknown effectiveness).

CBT plus drug treatments versus CBT alone One systematic review (search date 2005) added including a meta-analysis for short- and long-term outcomes. [66] Benefits and harms data enhanced. Categorisation of 'CBT plus antidepressants versus CBT alone (combination may be more effective in acute phase; unclear which is more effective with continued treatment, or 6 to 24 months after treatment discontinuation)' unchanged (Likely to be beneficial).

CBT versus other psychological treatments One RCT (73 people) added comparing CBT, exposure *in vivo*, and waiting list control. [26] It found no significant difference between CBT and exposure *in vivo* for a range of outcomes. One small RCT (49 people) added comparing CBT versus a self-help method supplied over the internet. [27] The RCT found no significant difference between groups for a range of outcome measures. Categorisation unchanged (Unknown effectiveness) as it is unclear how CBT compares with other psychological treatments.

Exposure (external or interoceptive) One RCT added (73 people) comparing exposure *in vivo*, CBT, and waiting list control. [26] It found no significant difference between exposure *in vivo* and CBT for a range of outcomes. Categorisation of 'Exposure (external or interoceptive)' unchanged (Likely to be beneficial).

Self-help One small RCT added (49 people) which compared a self-help method supplied over the internet versus CBT given in person. [27] The RCT found no significant difference between groups for a range of outcome measures. Categorisation of 'self-help (may be as effective as other forms of CBT)' unchanged (Likely to be beneficial).

CBT plus drug treatments versus drugs alone One systematic review (search date 2005) added which includes a meta-analysis for short- and long-term results. [66] Benefits and harms data enhanced. Categorisation changed. CBT plus antidepressants categorised as Likely to be beneficial compared with antidepressants alone as combination treatment may be more effective.

CBT versus drug treatments Existing evidence re-evaluated, and reporting in benefits section further enhanced with additional detail. Existing categorisation changed. 'CBT versus antidepressants (unclear which more effective, but weak evidence that effects of CBT may last longer than those of antidepressants)' categorised as Unknown effectiveness.

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Competing interests: SK attended a symposium organised and funded by Eli Lilly, the manufacturers of Fluoxetine (Prozac), Lundbeck, the manufacturers of Citalopram, and GSK Beecham, Wyeth pharmaceuticals, the manufacturers of Venlafaxine. DM declares that he has no competing interests.

Disclaimer

GRADE **Evaluation of interventions for Panic disorder.**

Important outcomes			Adverse effects, Quality of life, Symptom severity						
Studies (Participants)	**Outcome**	**Comparison**	**Type of evidence**	**Quality**	**Consistency**	**Directness**	**Effect size**	**GRADE**	**Comment**
What are the effects of non-drug treatments for panic disorder?									
at least 45 controlled studies (not clear) [17] [18] [19]	Symptom severity	CBT versus placebo or no treatment	4	–3	–1	–1	0	Very low	Quality points deducted for unclear randomisation, inclusion of studies other than RCTs, weak methods, and incomplete reporting of results. Consistency point deducted for conflicting results (depression). Directness point deducted for unclear outcome assessment
not clear (not clear) [18]	Quality of life	CBT versus placebo or no treatment	4	–3	0	–1	0	Very low	Quality points deducted for unclear randomisation, inclusion of studies other than RCTs, weak methods, and incomplete reporting of results. Directness point deducted for unclear outcome assessment
at least 17 clinical studies (not clear) [17] [18]	Symptom severity	CBT versus antidepressants	4	–3	0	–2	0	Very low	Quality points deducted for inclusion of studies other than RCTs, incomplete reporting of results, and uncertainty about significance of result (publication bias). Directness points deducted for inclusion of people taking benzodiazepines and unclear outcome assessment
26 controlled studies (not clear) [18]	Symptom severity	CBT versus behavioural therapy	4	–2	0	–1	0	Very low	Quality points deducted for inclusion of studies other than RCTs, and incomplete reporting of results. Directness point deducted for unclear outcome assessment
26 controlled studies (not clear) [18]	Quality of life	CBT versus behavioural therapy	4	–2	0	–1	0	Very low	Quality points deducted for inclusion of studies other than RCTs, and incomplete reporting of results. Directness point deducted for unclear outcome assessment
1 (73) [26]	Symptom severity	CBT versus exposure	4	–3	0	0	0	Very low	Quality points deducted for sparse data, incomplete reporting of results, and combining active treatment groups in statistical analysis
2 (96) [28] [29]	Symptom severity	Applied relaxation versus waiting list control	4	–3	0	–1	0	Very low	Quality points deducted for sparse data, incomplete reporting of results, and baseline differences between groups. Directness point deducted for composite outcome
5 (279) [30] [28] [29] [31] [29] [32]	Symptom severity	Applied relaxation versus CBT	4	–1	–1	–1	0	Very low	Quality point deducted for incomplete reporting of results. Consistency point deducted for conflicting results. Directness point deducted for co-intervention (self-exposure instructions)
1 (32) [29]	Symptom severity	Applied relaxation versus drug treatments	4	–2	0	0	0	Low	Quality points deducted for sparse data and incomplete reporting of results
2 (108) [34] [35]	Symptom severity	Client-centred therapy versus client-centred therapy plus exposure	4	–2	–1	–2	0	Very low	Quality points deducted for sparse data, and incomplete reporting of results. Consistency point deducted for different results for different outcomes. Directness points deducted for inclusion of people with different disease severity and unclear outcome assessment

Important outcomes			Adverse effects, Quality of life, Symptom severity						
Studies (Participants)	**Outcome**	**Comparison**	**Type of evidence**	**Quality**	**Consistency**	**Directness**	**Effect size**	**GRADE**	**Comment**
unclear (unclear) [17] [16]	Symptom severity	Cognitive restructuring plus interoceptive exposure compared with waiting list, pill placebo, or psychological placebo	4	–2	0	–2	0	Very low	Quality points deducted for incomplete reporting of results, and unclear reporting of studies included in analysis. Directness points deducted for inclusion of co-intervention and unclear outcome assessment
at least 1 (at least 28) [36] [17]	Symptom severity	Cognitive restructuring versus exposure	4	–2	0	–2	0	Very low	Quality points deducted for incomplete reporting of results, and unclear reporting of studies included in analysis. Directness points deducted for no direct statistical analysis between groups in one analysis and unclear outcome assessment in review
at least 2 (at least 234) [19] [22] [38] [39]	Symptom severity	Exposure versus control	4	–2	0	–1	0	Very low	Quality points deducted for incomplete reporting of results, and unclear reporting of studies included in analysis in one review. Directness points deducted for co-intervention in placebo group (relaxation therapy)
at least 8 clinical/controlled studies (not clear) [18]	Symptom severity	Self-help methods versus no treatment	4	–3	0	–1	0	Very low	Quality points deducted for inclusion of non-RCT data, incomplete reporting of results, and unclear reporting of studies included in analysis. Directness point deducted for combined control group (no treatment, pill, or therapy placebo)
3 (107) [41] [27] [23]	Symptom severity	Self-help methods versus CBT	4	–3	0	–1	0	Very low	Quality points deducted for incomplete reporting of results, inclusion of non-RCT data in analysis, and unclear reporting of studies included in analysis. Directness points deducted for no direct statistical comparison between groups in two studies
1 (45) [24]	Symptom severity	Breathing retraining plus CBT versus control	4	–2	0	–1	0	Very low	Quality points deducted for sparse data, and incomplete reporting of results. Directness point deducted for inclusion of co-intervention (CBT)
1 (45) [24]	Symptom severity	Breathing retraining plus CBT versus CBT alone	4	–2	0	0	0	Low	Quality points deducted for sparse data, and incomplete reporting of results
1 (40) [43]	Symptom severity	Brief dynamic psychotherapy plus clomipramine versus clomipramine alone	4	–2	0	–1	0	Very low	Quality points deducted for sparse data, and incomplete reporting of results. Directness point deducted for no statistical comparison between groups for some outcomes
1 (49) [33]	Symptom severity	Panic-focused psychodynamic psychotherapy versus applied relaxation	4	–2	0	–1	0	Very low	Quality points deducted for sparse data, and incomplete reporting. Directness point deducted for high rate of dropout in one group (significantly higher than other group)
3 (82) [45] [46] [47]	Symptom severity	Different forms of couple therapy versus each other	4	–2	0	0	0	Low	Quality points deducted for sparse data, and incomplete reporting of results

What are the effects of drug treatments for panic disorder?

Important outcomes			Adverse effects, Quality of life, Symptom severity						
Studies (Participants)	**Outcome**	**Comparison**	**Type of evidence**	**Quality**	**Consistency**	**Directness**	**Effect size**	**GRADE**	**Comment**
92 controlled studies, of which at least 2 were RCTs (at least 461) [18] [19] [51] [52]	Symptom severity	SSRIs versus placebo	4	–3	0	–2	0	Very low	Quality points deducted for incomplete reporting of results, inclusion of non-RCT data, and unclear reporting of studies included in analysis. Directness points deducted for use of treatment responders in one RCT, unclear measurement of outcome, and no direct statistical analysis between groups in some studies
91 controlled studies, of which at least 2 were RCTs (unclear, at least 237) [18] [19] [57] [58]	Symptom severity	Tricyclic antidepressants versus placebo	4	–3	0	–1	0	Very low	Quality points deducted for incomplete reporting of results, inclusion of non-RCT data, and unclear reporting of studies included in analysis. Directness point deducted for no statistical comparison between groups in some studies
At least 89 controlled studies, of which at least 17 were RCTs (at least 2284) [18] [61] [19]	Symptom severity	Benzodiazepines versus placebo	4	–3	0	–1	0	Very low	Quality points deducted for incomplete reporting of results, inclusion of non-RCT data, and unclear reporting of studies included in analysis. Directness point deducted for no statistical comparison between groups in some studies
2 (89) [63] [64]	Symptom severity	Oral buspirone plus CBT versus placebo plus CBT	4	–2	–1	0	0	Very low	Quality points deducted for sparse data and incomplete reporting of results. Consistency point deducted for conflicting results
1 (366) [65]	Symptom severity	MAOIs versus SSRIs	4	–1	0	–1	0	Low	Quality point deducted for incomplete reporting of results. Directness point deducted for small number of comparisons
What are the effects of combined drug and psychological treatments for panic disorder?									
at least 9 RCTs (at least 709) [18] [66]	Symptom severity	CBT plus antidepressants versus CBT alone	4	–3	–1	–1	0	Very low	Quality points deducted for incomplete reporting of results, unclear reporting of studies included in one analysis, inclusion of behavioural therapy in one analysis, and possible publication bias. Consistency point deducted for inconsistent results with different outcomes and over different time periods. Directness point deducted for limited generalisability
20 studies (not clear) [18]	Quality of life	CBT plus antidepressants versus CBT alone	4	–3	0	0	0	Very low	Quality points deducted for incomplete reporting of results, unclear reporting of studies included in analysis, inclusion of behavioural therapy, and possible publication bias
6 (604) [66]	Adverse effects	CBT plus antidepressants versus CBT alone	4	–1	0	–1	0	Low	Quality point deduced for combined analysis in control group. Directness point deducted for generalisability of results
at least 10 RCTs (at least 336) [67] [66] [68]	Symptom severity	CBT plus antidepressants versus antidepressants alone	4	–2	0	–1	0	Very low	Quality points deducted for incomplete reporting of results, inclusion of co-intervention (benzodiazepines) in one study. Directness point deducted for limited generalisability

We initially allocate 4 points to evidence from RCTs, and 2 points to evidence from observational studies. To attain the final GRADE score for a given comparison, points are deducted or added from this initial score based on preset criteria relating to the categories of quality, directness, consistency, and effect size. Quality: based on issues affecting methodological rigour (e.g., incomplete reporting of results, quasi-randomisation, sparse data [<200 people in the analysis]). Consistency: based on similarity of results across studies. Directness: based on generalisability of population or outcomes. Effect size: based on magnitude of effect as measured by statistics such as relative risk, odds ratio, or hazard ratio.